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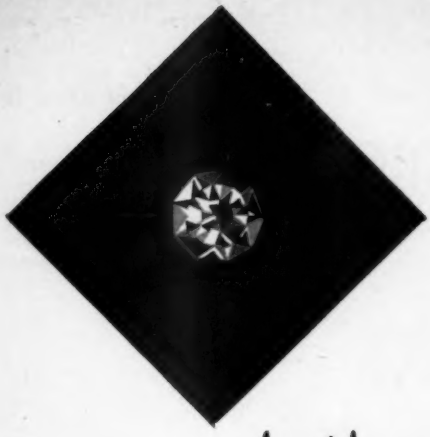

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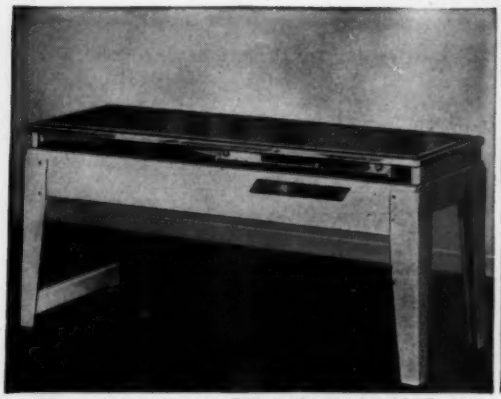

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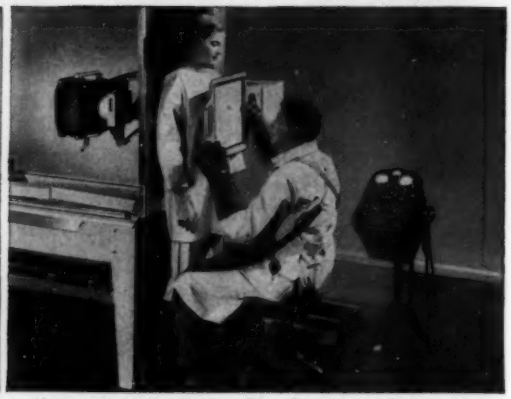

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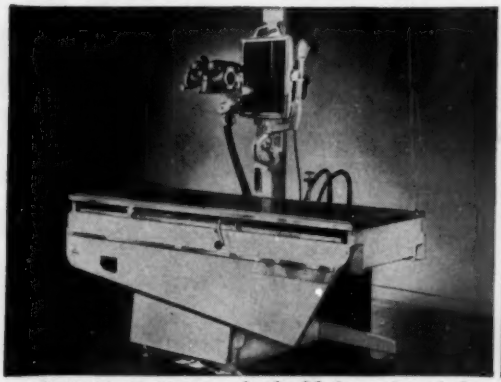

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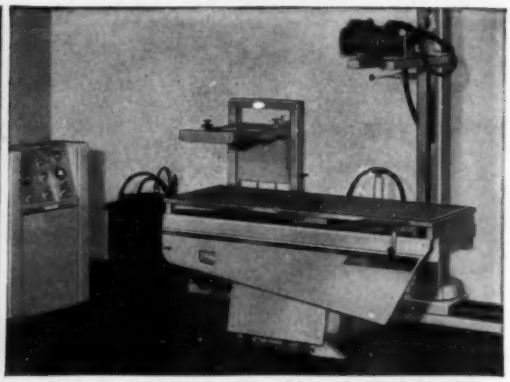

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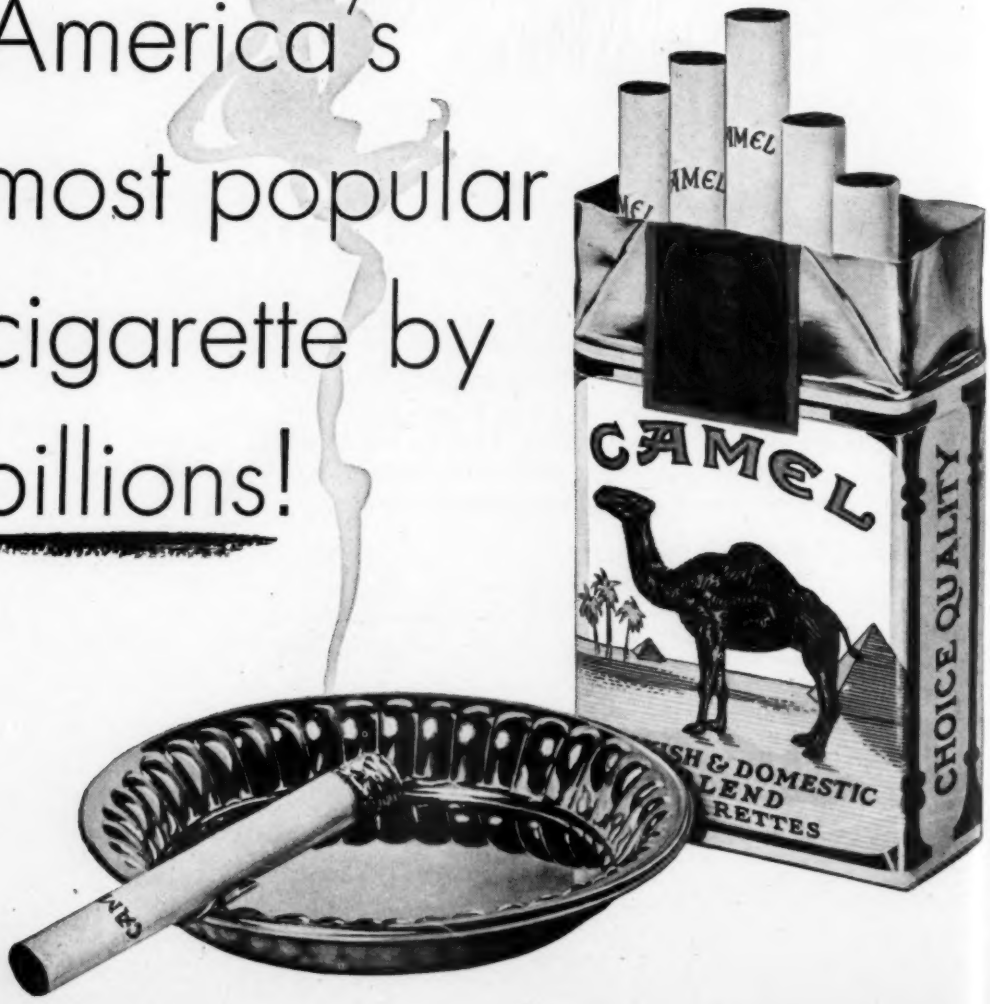

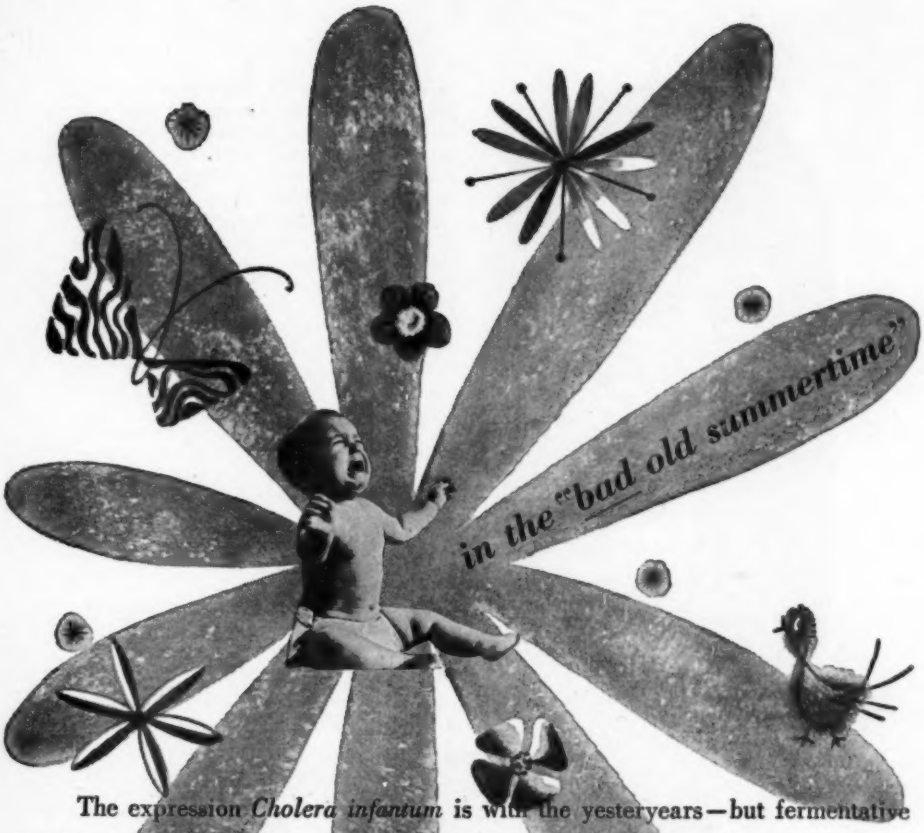

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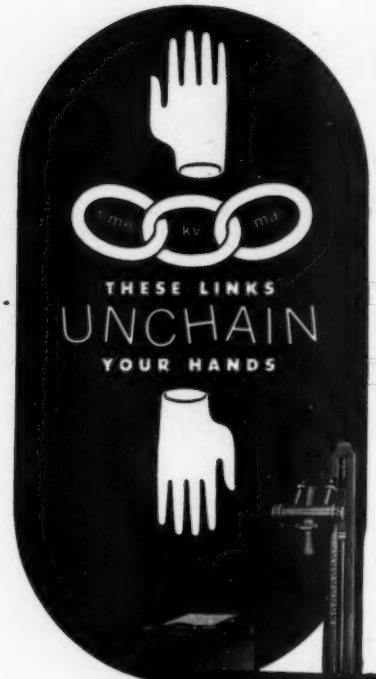

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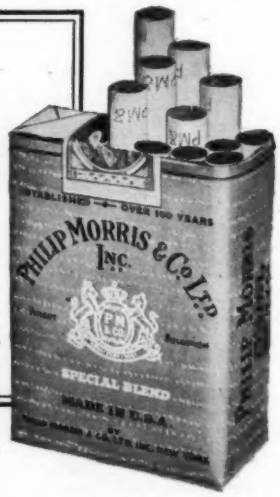

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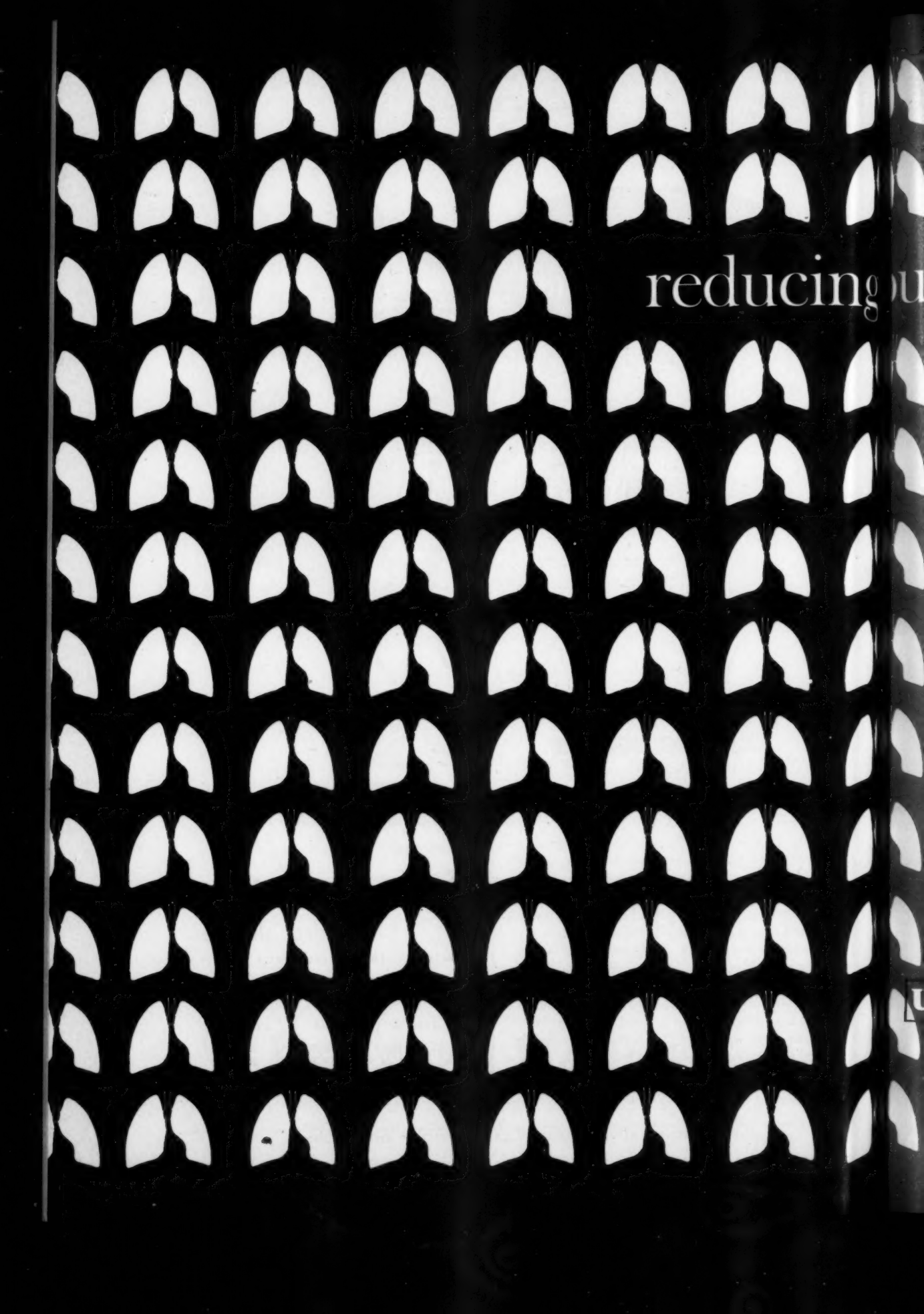
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1. Bauer, Gunnar: *Nine Years' Experience with Heparin in Acute Venous Thrombosis. Angiology, Vol. 1, No. 2, (Apr.) 1950.*

2. Stulz, William J.: *Long-Acting Heparin Preparation: A Useful Adjunct in Anticoagulant Therapy. U. S. Armed Forces Med. J., Vol. II, No. 1 (Jan.) 1951.*

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REFERENCES:

1. Bicknell, F. and Prescott, F.: The Vitamins in Medicine, 2nd ed., Heinemann, 1946.
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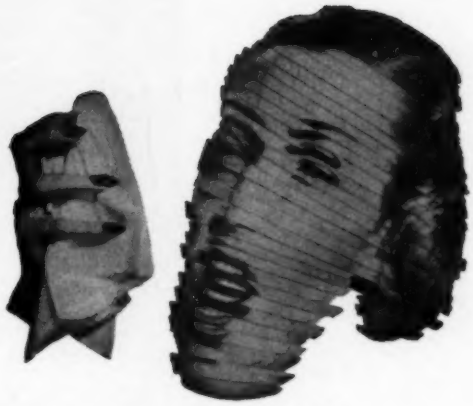

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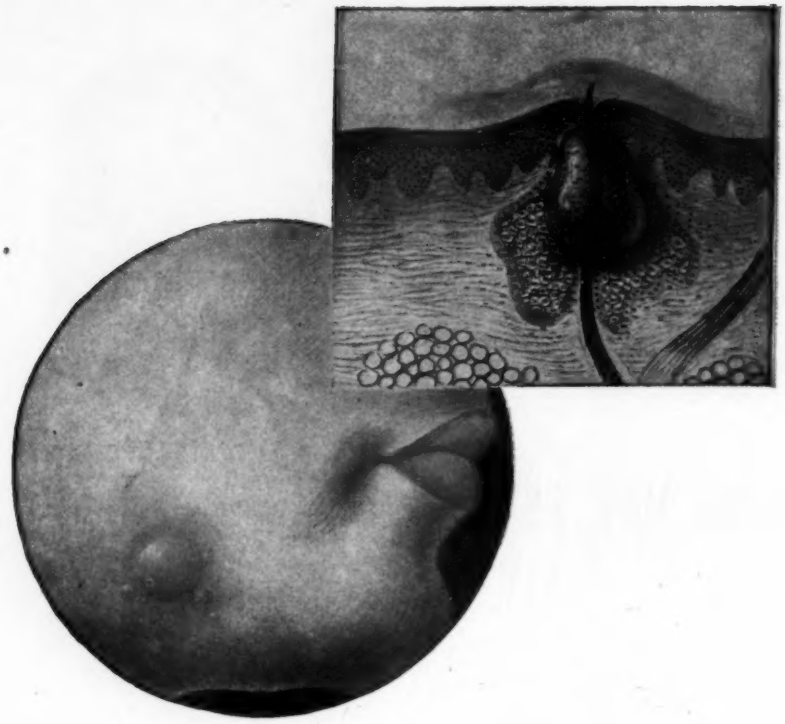

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Wright, L. T., et al.: Antibiotics and Chemotherapy 1:165 (June) 1951.

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Acute catarrhal conjunctivitis
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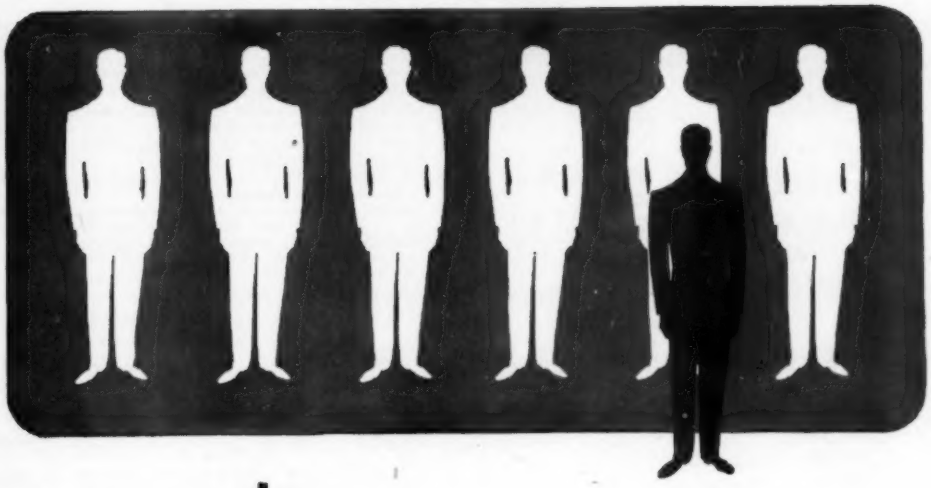

no symptoms

but *all* 34 patients in this study carried Endamoeba histolytica[1] in their stools! Five were classified as asymptomatic and 18 were "persons with such poorly defined symptoms that they would not normally seek medical assistance...," but a stool examination proved that all had amebic dysentery.

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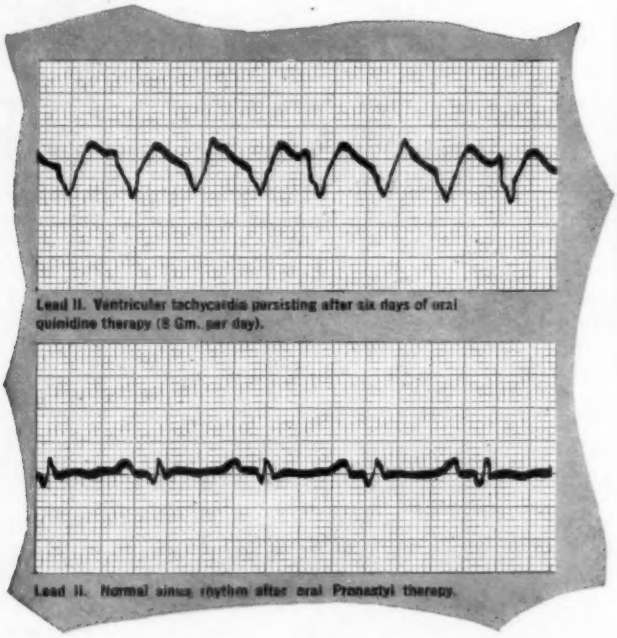

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Head Pain as a Diagnostic Lead

Frequently the presence of head pain is overlooked. The physician learns of it only if he has made an effort to elicit the information. Since the etiology of the pain is the basis of rational management, the patient should be warned against taking medication before diagnosis is made.

Friedman[1] deplores the tendency to call any chronic recurring headache migraine. Careful history-taking and full physical and neurological examinations are essential for accurate diagnosis. A good starting point is a description of the headache — its character, laterality, frequency and intensity.[2]

The following chart gives briefly the primary diagnostic leads and treatment for the most common types of headache.

Etiology of Headache	Primary Diagnostic Data	Primary Therapy
Inflammatory e.g., Meningitis Abscess	Inflammation of intracranial structures; fever; leucocytosis; bacteriologic diag.	Specific: sulfonamides and antibiotics. Symptomatic: analgesics.
Tumor	Pain varies as spinal press. changes; skull X-ray.	Specific: surgery. Symptomatic, analgesics &/or hypnotics.
Sinusitis	Sinus congestion and infection; cloudy X-ray.	Specific: antibiotics and drainage. Symptomatic: analgesics.
Hypertensive	Hypertension present but pain not related to b. p. level; Dihydroergotamine. relieves pain.	General hypertension therapy; sedation. Symptomatic: analgesics.
Migraine & other vascular headaches	Headache: recurrent, intense, throbbing. No organic caussation; migraine in family; patient: energetic, perfectionist. Visual prodromata; g-i. upset during headache.	To abort attack: oral ergotamine plus caffeine. General: adjustment to minimize nervous stress.

Data here tabulated is from: Wolf, G., Jr.,[3] and Friedman, A. P.[4]

Cecil[5] ranks vascular headaches, e.g., migraine and tension headaches, as the most commonly encountered of all. Because of their functional nature and usual recurrence at frequent intervals, they present a long-term therapeutic problem.

Therapy is conducted along two lines:

1) Psychotherapy to reduce the frequency of attacks. This consists mainly of advice on emotional adjustment to stressful situations and guidance toward a good balance between work and relaxation.

2) Treatment of the distressing attack to prevent the usual period of incapacitation. Many investigators have reported that ergotamine preparations are effective for relief of the acute migraine attack in 80% of cases.[1,6] *The drug is given immediately when an attack is approaching and dosage adjusted to the needs of the individual.*

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ARIZONA MEDICINE

Journal of ARIZONA MEDICAL ASSOCIATION

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ORIGINAL ARTICLES

THE CLINICAL APPLICATION OF CORTISONE AND ACTH IN ARTHRITIS AND RELATED CONDITIONS: METHODS AND PROBLEMS

PART II: SIDE-EFFECTS, COMPLICATIONS, CONTRAINDICATIONS, PRECAUTIONS AND CONCLUSIONS

By

Otto Steinbrocker, M.D., Mortimer E. Ehrlich, M.D., Murray Silver, M.D., William Sicher, M.D., Sidney Berkowitz, M.D., Solomon Carp, M.D., and Harold Feinstein, M.D.

From the Arthritis Department of the Hospital for Joint Diseases and Lenox Hill Hospital, New York, N. Y.

Presented by the senior author before the Arizona Medical Association, May 1st and 2nd, 1951

SIDE-EFFECTS AND COMPLICATIONS WITH ACTH AND CORTISONE

In the course of both short- and long-term administration of cortisone and ACTH in 140 cases with arthritis and allied musculoskeletal conditions, the clinical observations previously discussed also included a variety of side-actions and complications. A presentation of the consequences of using these remarkable compounds must include the undesirable reactions as well as the usual, and often striking, benefits.(13) In this discussion of side-effects and complications, we have reserved the term "complications" for those pathologic states developing during the administration of ACTH and cortisone (without necessarily proving a causal relationship), which are not reversible after cessation of therapy, or for those reactions which constitute a threat to the patient's well-beilng or survival.

The side-effects and complications which appeared during the administration of the substances to our first 128 patients are listed in Table 7. The large number of reactions noted is due to multiple incidents in some cases. These benign or untoward effects occurred in about 40% of the patients in our series. Aproximately 90% of these side-actions were temporary, quickly reversible on discontinuance of therapy, or of no clinical importance.

Glycosuria occurred in 18 cases. It remained after interruption of the hormone in only two, and it is likely that they were patients with latent diabetes activated by the use of ACTH and cortisone. The glycosuria was transient in the other 16 cases and disappeared either following withdrawal of treatment, or during continued administration. In some patients the glycosuria was not associated with a hyperglycemia and it seemed to arise from a lowered renal threshhold.

Edema was seen in 16 cases. This required intervention with mercurial diuretics in only 8. In 2 patients cessation of therapy was imposed by the increasing edema. Occasionally eccentric swelling of a part, without peripheral pitting, is the only sign of invisible edema in patients gaining weight rapidly.

Rounding of facial and bodily contours was

encountered 12 times. This usually unimportant side-effect was seen most clearly and frequently in those patients on long-term programs.

The cutaneous side-effects included hirsutism, acneform lesions, diffuse or circumscribed miscellaneous eruptions (particularly erythematous), purpuric eruptions, striae and, in one patient, pigmentation of the nails. These integumental reactions occurred in 30 cases.

Menstrual disturbances were noted in 4 cases, with prolonged amenorrhea in 2. Impotence was reported by two male patients. However, in another male and in one female there was increased libido.

Seven patients developed gastro-intestinal disorders, only one of which was serious. This was in a case on ACTH who suffered a perforation of his duodenal ulcer before admission to our service. Two of the patients receiving the early preparations of ACTH complained of abdominal cramps and four on cortisone acquired stubborn constipation.

Psychic disturbances appeared in 24 cases. Fourteen patients became somewhat euphoric and four complained of insomnia. Although 7 patients exhibited psychotic symptoms at one time or another, these effects were temporary and disappeared promptly on cessation of therapy.

Sixteen instances of untoward cardiovascular and peripheral vascular manifestations were seen in 15 patients. Five of these developed transient hypertension, which did not require interruption of therapy. One patient had symptoms of coronary insufficiency and mild congestive failure during the use of cortisone, but he had experienced similar episodes before receiv- this compound.

Seven patients developed thrombophlebitis. Unilateral edema of an extremity, with suppressed external signs of local inflammation, may be the first ominous evidence of this complication. Bilateral femoral arterial occlusion occurred in one case. One patient developed a hemiplegia which cleared right after cessation of cortisone administration. Soon after its resumption, owing to a severe recurrence of polyarthritis, signs of cerebral thrombosis and diffuse encephalopathy became evident.

All but one of those presenting vascular complications were in their 6th to 8th decade of life. It is, therefore, quite possible that some of these serious developments were not causally related to the administration of ACTH or cortisone, but were coincidental developments. Their frequency in this series, however, seems to exced the ordinary expectancy of these events. This fact together with the reported changes in blood coagulation time(15) during the use of these compounds leads us to view these complications with some concern, while awaiting the accumulation of sufficient data to warrant more reliable interpretation.

Six patients exhibited signs and symptoms of a variety of neuropathies. Two cases developed a paresis of the extensor muscles of the 3rd and 4th fingers of one hand, while two others complained of paresthesias in the hands and feet. Another patient felt annoying symptoms along the course of one ulnar nerve. Paresthesias cleared when dosage schedules were lowered or discontinued. The sixth patient, not of particularly neurotic temperament, noted a gradual diminution of the sense of smell after 2 months of cortisone administration. The compound has been continued for a total of 7 months now with an apparently complete anosmia and some disturbance of taste. Here again, the frequency of neuropathies seems to exceed ordinary expectancy even in patients with rheumatoid arthritis.

Severe weakness and asthenia developed in three patients during treatment. Similar "withdrawal" symptoms occurred after discontinuance of cortisone in two cases, and ACTH in another.

That ACTH and cortisone are capable of producing a negative calcium balance is well known. Decalcification of bone, or aggravation of preexisting osteoporosis to an extent sufficient to lead to specific complications occurred in two of our patients. One with severe peripheral rheumatoid arthritis was doing very well on a prolonged maintenance program of cortisone. No spinal symptoms had been noted, although a mild pre-existant osteoporosis was seen. She suddenly developed acute dorsolumbar back pain, and a compression fracture of the 11th dorsal vertebra was found. Another patient was recovering from a "frozen shoulder" after an initial course of cortisone in the hospital. She sustained a fracture of the surgical neck of the humerus after five weeks of maintenance therapy at home. In her own words: "I brushed the door-frame with my arm while passing through a doorway." Pain was not severe, although it seemed out of proportion to the extent of the

injury. Roentgenograms revealed the unexpected fracture as well as increased osteoporosis of the upper end of the humerus.

CONTRAINDICATIONS TO ACTH AND CORTISONE

The prevention of side-effects and complications depends on a constant awareness of the tendency of these compounds toward a variety of undesirable effects. Some absolute and relative contraindications to their use now are recognized. These are listed:

Contraindications to ACTH and Cortisone

Extensive old tuberculous lesions; any early ones
Cardiac failure
Severe diabetes, difficult to control
Psychotic episodes.
Severe psychoneurosis
Severe hypertension
Infectious disease and suppuration
Malaria
Severe osteoporosis

Administered cautiously (if at all) in:

Diabetes mellitus
Mild hypertension
Cardiovascular disease, compensated
Severe varicosities, phlebothrombosis
Obliterative arterial disease
Osteoporosis, post-menopausal and senile
Neurosis

PRECAUTIONS IN ADMINISTERING ACTH AND CORTISONE

Our own observations have taught us that continual alertness and the avoidance of any sense of false security after a short experience without incident are essential to the use of these substances with the greatest safety. A complete history as well as thorough physical, laboratory, and roentgenographic evaluation of each patient's pretreatment condition is mandatory. We have learned that special attention must be given to the cardiovascular status, past tendency toward intravascular clotting, familial or personal history of diabetes mellitus, emotional instability, and any demineralization of bone. While Patients are under treatment, they must be followed closely and seen regularly as these compounds may greatly alter their reactivity to any purely coincidental intercurrent event. In that way any abnormalities possibly arising from the use of these materials may be detected early. The presence of relative contra-indications to the use of these compounds must be weighed carefully against their expected benefit in each case.

The fact that we have reported no instances of marked hypopotassemia (2, 12) may be due in part to the fact that our patients received supplemental potassium throughout therapy. Body weight, blood pressure readings, general physical and psychic assessments and other observations were made at frequent intervals, as outlined in our routine in a previous chapter.

The ability of these hormones to produce a wide variety of actions other than the useful therapeutic effects makes it necessary to administer them with due caution. It is desirable to discuss the matter tactfully with the patient or relative, and thereby share some of the responsibility involved. Accordingly, we employ the following physical and psychologic safeguards:

Special Precautions with ACTH and Cortisone

1. Hospitalization recommended for initial period.
   Imperative for elderly patients and those with coincidental disease.
2. A signed release, but no longer required by us.
3. Explanation of suppressive effects (not cure); Probably prolonged maintenance, particularly in chronic disease
4. Costs during initial period and for maintenance, frankly estimated for drugs, tests, and services.
5. Side-effects discussed with patient:
   Benign
   Undesirable
   Complications
6. In elderly patients especially, note and recheck of:
   Glycosuria and hyperglycemia
   Cardiovascular competence
   Varicosities
   Peripheral pulses
   Emotional deviations
   Demineralization

COMBINED THERAPY WITH ACTH AND CORTISONE

To prevent or counteract some of the undesirable reactions to the administration of these compounds a number of therapeutic complements are being employed. Some of these are intended to correct deficiencies associated with the use of these new drugs, others to enhance control of symptoms and in that way possibly to reduce the amount of the substance required, or perhaps even to replace it. Among those utilized, or under study, are:

Some Therapeutic Complements Used with ACTH and Cortisone Compensatory
- Potassium chloride
- Estrogens
- Androgens
- Thyroid extract
- Dicumarol

Synergistic
- Vitamin concentrates (ascorbic acid)
- Analgesics (salicylates, codeine, etc.)
- Gold salts
- Intermediate stseroids
- Physical modalities

The value of some of these agents is controversial. KCI medication generally is included to minimize any tendency toward hypopotassemia, but its place is not unanimously conceded. The use of androgens and estrogens in the prevention of demineralization is still under study. When introduced for this purpose, the methods of Albright and Reifenstein are followed with regard to dosage, route and intervals.(16) Certainly, females already subject to menopausal symptoms, or those suffering from such newly precipitated or aggravated complaints during therapy with ACTH or cortisone, should receive supplementary sex hormones to control those particular features.

Thyroid extract is under study in those patients receiving ACTH and cortisone who develop a type of obesity and other features suggestive of hypothyroidism. The additive value of this substance has not been clearly demonstrated as yet.

Dicumarol is being employed in patients developing vascular complications. When, for good reasons, ACTH or cortisone is to be utilized in individuals known to have suffered thrombovascular, or occlusive episodes, the addition of the anti-coagulant is justified.

The introduction of ascorbic acid in the management program of patients getting the new compounds has not produced any recognizable benefits in our limited experience with this innovation. Gold salts are being combined with cortisone in simultaneous and other techniques but, up to the present time at least, it appears that chrysotherapy adds no advantage over the use of either agent alone.(2, 17) This may not prove to be true of ACTH, although too limited evidence of combined effectiveness is available to date for any conclusions.(18)

Analgesics, usually salicylates and/or codeine, frequently are prescribed in ordinarily adequate doses before raising the amount of ACTH or cortisone during the maintenance period. Sometimes the need for increasing the maintenance level of the latter compounds appears to be postponed for small or long intervals. Heat modalities are apt to provide their ordinary temporary pallation and help to tide patients over a mild period of transient "rebound symptoms." The use of suitable exercises, with due caution to avoid strain, probably constitutes the most helpful physiotherapeutic measure. Intermediate steroids, such as pregnenolone and actoxy-pregnenolone have failed in our limited experience to provide any impressive complementary or substitutive action.

DISCUSSION

ACTH and cortisone have amply confirmed the observations of Hench and his coworkers that these compounds are the most potent suppressants of the features of rheumatoid arthritis by their effects on the clinical and laboratory signs of this disease. We have noted similar suppressive action in other musculoskeletal conditions, some of which have been reported by them and others. The striking control of locomotor symptoms provided by these substances must be balanced by the knowledge of the frequently temporary nature of their benefits, as well as their potential for producing annoying and sometimes serious reactions. The widespread influence of these powerful hormones on the metabolic processes of the body probably accounts for the diversity of side-effects and complications which may accompany their therapeutic activity. The clinical versatility of these compounds is evidenced by the list of symptom-producng mechanisms which respond to their use. These include inflammatory processes as in rheumatoid arthritis; metabolic disturbances as in gout; degenerative disorders as in degenerative arthritis, irritative and traumatic reactions as in periarthritis and in calcific tendonitis; and, apparently, neurovascular mechanisms as in the shoulder-hand syndrome.

The predominent clinical effects of ACTH and cortisone on this wide spectrum of pathogenetic processes in musculoskeletal disorders may be classified as anti-inflammatory, analgesic, antipyretic, anti-allergic, anti-fibroblastic and altered tissue membrance permeability. The primary questions that repeatedly arise while ad-

ministering the preparations are: Can all of these varied clinical consequences be explained by a single form of chemico-physiologic action affecting the reactivity of the connective tissue of supportive structures to any of a host of insulting agents; or, do they reflect a wide multiplicity of actions of the hormones in various forms of pathologic physiology? Are the observed effects due to a peripheral action alone, or are associated central, visceral and peripheral responses involved in the outcome? These questions bearing on the more exact manner in which these compounds control symptoms have not been clarified as yet.

Whatever the answers to these questions may prove to be, our limited experience suggests that the clinical application of ACTH and cortisone to musculoskeletal disorders may be classified practically from a broad therapeutic standpoint, according to the special considerations involved, into three major groups:

Acute Rheumatic and Locomotor conditions responsive to ACTH and Cortisone:

- Acute rheumatic fever
- Acute calcific tendonitis and bursitis
- Acute gout (colchicine-resistant)
- Collagen diseases (early)
  - Lupus erythematosis, dermatomyositis, scleroderma, periarteritis nodosa.

Chronic, relatively self-limiting:

- Reflex dystrophy (including shoulder-hand syndrome)
- Periarthritis of the shoulder
- Chronic calcific tendonitis and bursitis (?)

Chronic Progressive:

- Rheumatoid arthritis
- Rheumatoid-like arthropathies
  - Ankylosing spondylitis, psoriatic, etc.
- Chronic collagen diseases
- Degenerative arthritis

In the acute processes enumerated, ACTH and cortisone have produced impressive benefits. Their effectiveness has been studied so far on a rather limited investigative basis. In such serious diseases as rheumatic fever and the collagen complexes, they certainly merit a more thorough trial. In the others on our list of acute disturbances, colchicine-resistant gout and acute tendonitis and bursitis, the need for only short-term therapy makes their use worthy of more extensive study.

These new substances may make a helpful place for themselves in some stubborn conditions which are relatively self-limiting, such as periarthritis and reflex dystrophy. In these, the prompt relief of discomfort and the shortening of the clinical course would be worthy contributions, if borne out in larger series. Administration of the new hormones here for relatively short periods probably avoids some of the ill-effects of long-term therapy.

In the last group, the chronic progressive conditions, therapy with ACTH and cortisone requires long-term administration, for an indefinite time. It is in these diseases, for which the indications usually are most compelling, that the role of ACTH and cortisone as therapeutic agents creates the most questions and problems regarding their adequacy and possible hazards.

The observations made here and those presented in the current literature naturally reflect the discernable responses and reactions during the comparatively short time that ACTH and cortisone have been available. It is quite likely that, as further information is collected on the clinical behavior and the possible pathologic effects of these compounds, our understanding of their proper and efficient application in investigation and therapy will continue to be augmented. Obviously, a balanced evaluation of the place that ACTH and cortisone may assume in our medical resources cannot be made until we have acquired this fuller knowledge of the range and circumstances of the responses and the reactions they may produce. Until then, the selective and cautious use of these substances in rheumatoid arthritis, in rheumatoid-like diseases, and in certain other acute and refractory conditions, is warranted after a mutual understanding of the factors involved, as well as the alert and meticulous management required.

The isolation of compound E undoubtedly is one of the great biochemical achievements of our day, opening a new era in that phase of medicine. The application of cortisone and ACTH to rheumatoid disease constitutes an epochal clinical contribution with limitless prospects for new lines of research and practical usefulness. These developments already have inspired the most widespread and intensive interest and investigation of the rheumatic disorders in the history of medicine. Methods of applying these new hormones by the most effective and satisfactory techniques are under wide study. It is no disparagement to state that great

efforts are being directed to the discovery of substances with "cortisone-like" or "ACTH-like" properties, yet free of the tendency of these compounds toward undesirable reactions, or to find some way of combining them simultaneously with another agent toward the same ends. It is to be hoped these objectives soon will be achieved, in one way or another, so that the great advantages of ACTH and cortisone may be utilized to the fullest.

SUMMARY AND CONCLUSION

1. ACTH and cortisone have produced the most rapid and effective reversal of symptoms and signs in our series of 72 patients with rheumatoid arthritis and in 27 with rheumatoid-like articular diseases.

2. Almost all cases of rheumatoid arthritis and rheumatoid-like arthropathies responded initially to some degree and the greater majority retained their improvement on maintenance therapy. With prolonged treatment, a small but gradually increasing number became less responsive, or developed undesirable side-effects or complications.

3. In our small series of twelve cases of degenerative arthritis of the hip, relief of pain and improvement in coordinated movements were produced in nine, although increased motion at the hip occurred in only two of these. As in rheumatoid arthritis, indefinite periods of maintenance therapy have been required to sustain beneficial effects. The trend of response has been favorable in this small group which, however, is too meagre for final deductions at this time.

4. In self-limiting, non-rheumatoid locomotor disorders, such as periarthritis of the shoulder (frozen shoulder) and reflex dystrophy (shoulder-hand syndrome) pain-relief and recovery of motion were impressive in most of the cases receiving cortisone or ACTH. Some of these patients retained their benefit without relapse after relatively short maintenance periods. Application of the new compounds to these self-limiting conditions, therefore, warrants further investigation.

5. Somewhat less than ⅓ of the patients in our series developed side-effects or untoward reactions. About 90% of these incidents were of no clinical importance. The vascular complications, the fractures, the psychoses and the neuropathies were the most troublesome and most often necessitated interruption of therapy.

6. Insufficient time has elapsed to properly evaluate the full potential of cortisone and ACTH for beneficial responses and undesirable

TABLE 7

Side-Effects and Complications of ACTH and Cortisone in 128 cases during Short- and Long-Term Administration

METABOLIC		**PSYCHIC ABNORMALITIES**	
Glycosuria (transient in 16)	18	Euphoria	14
Edema (peripheral)	16	Psychotic symptoms	7
Rounding of face and body	12	Insomnia	4
CUTANEOUS		**CARDIOVASCULAR**	
Hirsutism	9	Hypertension (transient)	5
Acne	8	Congestive failure	1
Miscellaneous	6	Coronary insuff.	1
Purpuric eruptions	4	Hemiplegia (transient)	1
Striae	2	Peripheral arterial occlusion	1
Pigmentation of nails	1	Thrombophlebitis	7
MENSTRUAL DISORDERS	4	**NEUROPATHIC**	6
GASTROINTESTINAL		**SKELETAL (Osteoporosis)**	
Perforation of ulcer (duod.)	1	Vertebral compression	1
Constipation	4	Fracture	1
Abdominal cramps (ACTH)	2		

reactions, particularly in relation to long-term administration in chronic, musculoskeletal disease. A balanced final appraisal of their role as practical therapeutic agents, therefore, must await further data on the range of clinical effects and possible pathologic changes produced by these substances in larger groups of cases during longer periods of observation.

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BASIC SCIENCE SEMINAR

THE PHARMACOLOGY OF ACTH AND CORTISONE

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I. INTRODUCTION

Published reports of clinical and experimental work dealing with ACTH and Cortisone have reached an almost overwhelming volume in recent months. It is hoped that this paper may be of some assistance in the task of keeping abreast of developments in this rapidly expanding field. However, a special attempt will be made to adhere chiefly to basic concepts rather than to discuss the clinical application of these hormones.

II. HISTORICAL SKETCH: DISCOVERY, DEVELOPMENT AND ISOLATION OF ACTH AND CORTISONE

It is just one hundred years ago that Thomas Addison first classically described the disease syndrome which results from the destruction or nonfunction of the adrenal gland in the human being. Thus, he noted the pigmentation, asthenia, and anorexia characteristic of the syndrome, and was aware of the extreme ease with which these patients became suddenly and critically ill, and, in fact, often died from minor infections and stresses of various types.

The adrenal cortex is the last of the ductless glands to yield its secrets to the investigator. As for the adrenocorticotropic (ACTH) hormone, it was Evans (1) who twenty-five years ago first reported that a pituitary extract prevented the atrophy of the adrenal gland which results from the removal of the pituitary gland in animals. Fifteen years of bioassay followed and until a quantitative method of bioassay for ACTH was achieved by Li and workers, and Sayers and workers in 1943 it was not possible for physiologists to study the effect of ACTH stimulation on the adrenal gland. Even more practical methods were found for performing the bioassay in the Armour Laboratories enabling large scale production of purified ACTH. Clinical use of their preparation in man to a large extent was first studied by Thorn (2) and Albright (3) and their associates in 1947.

It was during the last decade that increasingly more potent adrenal cortical extracts were being prepared. After five years of work attempting to extract adrenocortical hormones, Mason, Meyers, and Kendall isolated Compound E in 1935 (4). However, it was not until 1945 that the first large sample was obtained, and when given to patients who had Addison's disease it was found to be of little value. Interest in the hormones of the adrenal cortex sank to a very low level, and there was no assurance that large-scale production of Compound E was worthwhile.

In April, 1948, Sarett (5) discovered an improved method to synthesize Compound E, thus, raising the final yield nearly a hundred-fold. When a few grams were on hand, a conference was called between Merck & Company, Inc., and a group of clinicians to consider how the material should be used. It was at this meeting that Doctors Hench (6) and Kendall attempted to state a raionale for the use of Compound E in rheumatoid arthritis. As early as 1929 and 1931 Doctor Hench made two observations about rheumatoid arthritis which led him to believe that this disease was potentially reversible. He noted that pregnancy and jaundice in the female, and jaundice in the male who had rheumatoid arthritis were temporarily relieved. A bisexual hormone was suspected. It was also noted that pregnancy and jaundice temporarily relieved such non-rheumatic conditions as hay-fever, asthma, sensitivity to egg, migraine, and psoriasis. Hence, it was concluded that this phenomenon of relief was not disease-specific-but group-specific. Among the substances which they considered in 1938 was listed adrenal cortical extract. Along these lines, therefore, Compound E was first injected into a patient with rheumatoid arthritis on September 21, 1948. The effect of Compound E on rheumatoid arthritis was reported on April 13, 1947 (7), and shortly thereafter, there were rumors of a sharp increase in the sale of Vitamin E. For this reason, it seemed desirable to give Compound E a distinctive name. Hench and Kendall chose the name "Cortisone."

III. CHEMICAL STRUCTURE OF THE CORTICAL STEROIDS AND THE RELATION TO PHYSIOLOGICAL ACTIVITY.

Of the twenty-eight chemically-pure compounds which have been isolated from the adrenal cortex, only six appear to have the physiological activity of the adrenal cortex. Others

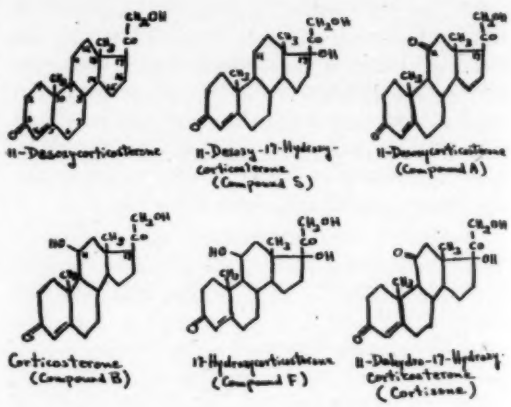

Figure I.-Steroids with known physiologic activity isolated from adrenal cortical tissue.

have sex activity and as for the remainder, the amounts have been too small for clinical investigation. The six adrenal corticoids are illustrated in Figure I. They all possess the following chemical groupings in common:

a. A ketogenic oxygen at the C-3 position
b. A double bond between C-4 and C-5
c. A side chain at C-17 which carries a ketone adjacent to a primary alcohol (the alpha-ketol groupings, as in fructose).

Also, it is to be noted that the two desoxy compounds are characterized by the absence of oxygen substituted in the C-11 position. The remaining four steroids are characterized by the presence of an atom of oxygen, either a ketone or a hydroxyform, at the C-11 position. These compounds are variously called 11-oxysteroids, oxygenated C-11 steroids or sometimes simply corticosterones.

Dehydrocorticosterone, corticosterone, and cortisone were synthesized from desovycholic acid, a constituent of bile.

The relationship between physiologic activity and chemical configuration among the adrenal corticoids is indeed very interesting. For example, 11-desoxycorticosterone whose major difference from the Compound F-like steroids is the absence of oxygen at C-11 position, effects electrolyte metabolism mainly. It has no effect on carbohydrate, protein, or fat metabolism. Neither does it effect the cellular elements of the blood or tissues. On the other hand, 11-oxysteroids are chiefly concerned with the metabolism of carbohydrate, protein, and fat. The C-11 oxygenated steroids also exert a definite

effect upon the hematopoietic system and tissue cells.

In respect to physiological activities, what are adrenocorticotropic hormone, and Cortisone? As most of you know, ACTH is a protein substance of high molecular weight (20,000) produced by the anterior pituitary. Relatively recently, Li (8) has shown that a protein-free peptide mixture prepared from whole adrenocorticotropic hormone has been found to have a high degree of adrenocorticotropic activity. The exact size of this peptide is not exactly known, but appears to be in the neighborhood of 1,000. In this range synthesis is not only possible but probable. ACTH has but one function, and that is to stimulate the adrenal cortex to function. When stimulated, the adrenal cortex produces many steroidal hormones, and now we know that they are chiefly Compound F-like steroids with possibly only traces of Cortisone. Chemically, therefore, ACTH and Cortisone are entirely different, and the common denominator in their effectiveness against a wide variety of disease states is the activity of Compound F-like hormones.

IV. THE ALARM REACTION AND GENERAL ADAPTATION SYNDROME

A. *The Alarm Reaction*:

"The alarm reaction", as a clearly defined separate entity, was first described by Selye in 1936 (9), and because of its close association with the role of ACTH and Cortisone it becomes important that an understanding of this phenomenon be obtained.

It was realized that in response to a great variety of toxic agents the organism responds with the same set of symptoms. The reaction consists of two more-or-less distinct phases, and it is initiated by an acute "stress" situation, such as trauma, surgery, infection, etc. . . See Figure II. The first or "shock phase" is characterized by: tachycardia, decrease in muscular tone and body temperature, formation of gastric or duodenal ulcers, hemoconcentration, anuria, edema formation, decrease in blood chlorides, acidosis, and a transitory rise followed by a decrease in blood sugar, leukopenia followed by leukocytosis, and a discharge of adrenalin from the adrenal medulla. It is the stimulation of the anterior pituitary gland to put out ACTH which in turn stimulates the adrenal cortex to secrete its protective corticoids that counterbalances the effect of the "shock phase." This phase may last anywhere from a few minutes to twenty-four hours, and unless the termination is fatal, it is followed by a second or "counter-shock phase." There occurs a reversal of most signs characteristic of the shock phase. Thus, there is blood dilution and increase in blood volume, increase in blood sugar and blood chlorides, alkalosis, diuresis, and often a rise in body temperature.

If the animal is maintained under the stress or "alarming stimulus", as Selye, calls it, that produced the shock phase the counter-shock phase gradually merges into the "stage of resistance", during which most of the morphologic lesions regress and specific resistance reaches its peak.

Finally, it was found that even a perfectly adapted organism cannot indefinitely maintain itself in the stage of resistance. If exposure to abnormal condition continues adaptation wears out; the lesions characteristic of the alarm reaction as involulation of the lymphatic structures, adrenal enlargement, gastro-intestinal ulcers reappear and the "stage of exhaustion" develops during which further resistance becomes impossible and death ensues.

B. *General Adaptation Syndrome*:

Selye feels that when the pituitary-adrenal hormonal adaptation mechanism breaks down a variety of diseases may occur. He feels there is enough evidence to show that hypertension, nephrosclerosis and periarteritis are probably due to abnormal adaptive processes. Other diseases are also listed in order to call attention to their possible connection with the general adaptation syndrome. He produced morphologic lesions in the kidneys of experimental animals that were unilaterally nephrectomized and fed high protein and high salt diets which resembled nephrosclerosis; lesions in arteries resembling those of periarteritis nodosa; Aschoff bodies in the myocardium similar to those seen in rheumatic carditis; these changes were not infrequently associated with hypertension and arthritides. These changes were produced by the administration of large doses of pure syntheitc desoxycorticosterone acetate as well as anterior pituitary extracts. All experimental observations are most readily compatible with the view that during the general adaptation syndrome, certain hormones of the anterior pituitary and adrenal cortex are produced in excessive amounts in order to increase resistance; this defensive endocrine response is valuable in as much as it

facilitates adaptation to stress (i.e., infections, intoxications, nervous commotions, cold, etc. . .), but the resulting endogenous hormone overdosage with an imbalance of excess mineralocorticiods over glucocorticoids may become the cause of certain cardiovascular, renal and joint diseases. This, Selye has termed a "derailed" adaptive response. Therefore, administration of cortisone counterbalances the excess desoxycorticosterone-like steroid production resulting in a more normal adaptive response to stress. Thus developed the concept that many of the most common maladies of man are "diseases of adaptation", that is. to say, the by-products of abnormal adaptive reactions to stress.

V. METABOLIC AND PHYSIOLOGIC EFFECTS OF ADRENAL CORICAL STIMULATION

The metabolic and physiologic effects (Figure III) of adrenal cortical stimulation by ACTH suggests that there are possibly three different types of hormones secreted by the adrenal gland: namely,

A. *Desoxycorticosterone-like Hormones*:

This group of hormones causes retention of sodium and chloride with concurrent retention of fluids and decreased sweating. Increased excretion of potassium may result, to some extent from the displacement of intracellular potassium by the retained sodium.

Additional potassium loss may occur in the early phase of ACTH and Cortisone administration. This may be followed by a phase of potassium retention by the liver together with the increased glycogen deposition and finally there is an actual loss of intra-cellular potassium in the course of the establishment of a negative nitrogen balance due to increased protein breakdown. This anti-anabolic effect produced by excessive ACTH stimulation may be obviated in part by the anabolic action of testosterone or adrenal "androgens", and thus correct to some extent the increased excretion of potassium. Increased stimulation of the adrenal cortex by ACTH may produce a hypokalemic, hypochloremic alkalosis such as is seen in Cushing's syndrome from over-excretion of the potassium ion resulting in fatigue and electro-cardiographic changes characteristic of potassium deficiency.

Excessive adrenal cortical activity seems to withdraw calcium and phosphorus from bone into the extracellular fluids from which they are excreted into the urine and feces. This finding appears to be correlated with a fall in alkaline phosphatase. Decreased osteoid formation with less laying down of bone to explain these shifts has been reported. This may well explain the osteoporosis commonly seen in Cushing's syndrome. However, this has not been seen with doses now employed.

Compensating mechanisms come into play, causing most individuals to diurese retained fluids, sodium and chloride and begin to retain potassium while still on the same dose or when it is decreased. There is some evidence that the adrenal cortex can secrete corticoids that actually cause excretion of sodium and chloride and retention of potassium. This electrolyte effect and resulting edema is not serious if carefully observed for it may correct itself while on the same dose or it can be corrected by lowering the dose, omitting several doses or by putting the patient on a low salt, high potassium intake.

The Compound F-like hormones also have an electrolyte effect similar to the desoxycorticosterone-like hormones. However, the effect is less marked. The desoxycorticoids, on the other hand, have none of the metabolic or physiologic effects characteristic of the Compound F-like hormones.

B. *Compound F-like Hormones, or* 17 *Hydroxycorticosterone-like Steroids*:

There is evidence that the human adrenal cortex secretes Compound F-like hormones and not Cortisone, which is secreted only in trace amounts, if at all. These hormones affect the intermediary metabolism of carbohydrate, protein, and fat.

1. *Carbohydrate*:

They cause glyconeogenesis or conversion of glucose to glycogen in the liver and muscles to restore the glycogen stores that are used up in the "alarm reaction," or reaction to acute "stress" situations. Over-stimulation of the adrenal cortex may even produce glycosuria with or without hyperglycemia. Glycosuria without hyperglycemia has been interpreted as due to a lowering of the renal threshold. The glycosuria with hyperglycemia may result when utilization of glucose and formation and deposition of glycogen cannot keep pace with the rapid mobilization of sources of energy (as conversion of amino acids and possible fats to glucose) and their conversion to glucose. The hypoglycemia and glycosuria, therefore, are not indicative of a true diabetes, but merely represent too rapid

mobilization of energy sources. However, latent diabetes in those individuals with a family tendency are more prone to develop a diabetes-like state. It has been suggested that ACTH be used as a test to bring out this tendency in these cases when the diagnosis is questionable. This condition is relatively resistant to insulin as is similarly the diabetes seen in Cushing's syndrome. It only occurs on high doses of ACTH or Cortisone and it will disappear when the dose is lowered or the hormones stopped.

During ACTH therapy, fasting blood glutathione decreases as carbohydrate tolerance is lowered (10). Administration of reduced glutathione during a course of ACTH induced diabetes produces temporary cessation of glycosuria and a fall of blood sugar (11). Thus, glutathione antagonizes the diabetogenic effort of ACTH.

2. *Protein*:

Compound F-like steroids display an anti-anabolic effect by the mobilization of amino-acids from tissue proteins, partly as a source of energy, partly for conversion to glucose and glycogen (carbohydrate-sparing effect), and partly to make amino acids available for protein synthesis in injured or abnormal tissues. The extent to which a negative nitrogen balance is established depends upon the relative increase in the 11-oxysteroids and androgenic steroids under the action of ACTH in any given case. The creatinuria and increased excretion of uric acid would be compatible with this increased catabolism of protein.

3. *Fat*:

They also mobilize fat from the fat depots as a source of energy and possibly for conversion to glucose and glycogen (carbohydrate-sparing effect). There occurs an increased production and utilization of fat with a decrease in the respiratory quotient and other metabolic pathways of fat. After an initial transitory rise, this is reflected by a lack of ketone bodies in the blood and urine, as well as the absence of acidosis. In summary, the above effects of the excessively stimulated adrenal cortex is reflected in:

a. Increased excretion of nitrogen;
b. Increased excretion of potassium;
c. Increased excretion of phosphate;
d. Increased excretion of calcium.

Therefore, it becomes apparent that the main metabolic action of this group of the Compound F-like steroids is in the mobilization of sources of energy and restoring sources of energy in the form of glycogen in the body.

Studies still in progress at the Donner Laboratories with ACTH and Cortisone in atherosclerotic rabbits indicate striking changes in the serum levels of the various giant lipo-protein molecules (cholesterol-containing), which consists of an initial drop followed by a rise (12).

C. *Adrenal Corticoandrogens*:

Adrenosterone-like steroids are also secreted by the adrenal cortex and appear to have an anabolic function when contrasted with the catabolic effects of compound F-like hormones such as Cortisone. As judged by signs of masculinization in some individuals (especially dark skinned, hairy women), ACTH appears to increase the secretion of adrenosterone-like compounds. Adrenosterone-like corticoids may induce a positive nitrogen balance and increase body protein in contrast to Compound F-like hormones. The ratio of the amount secreted between these two groups of steroids by the adrenal cortex may be a major determining factor in the over-all effect of the adrenal cortical stimulation by ACTH on the total body proteins.

A close functional inter-relationship exists between the adrenal and thyroid glands. For a number of days ACTH may reduce the basal metabolism rate. This may be due to the inhibition of the pituitary thyroid stimulating hormone (TSH) and is reflected in a decreased rate of uptake of radioactive iodine by the thyroid and by a lowered plasma protein-bound iodine concentration—a measure of circulating thyroid hormone.

On the other hand, ACTH seems to exhibit a calorigenic effect through the stimulation of the secretion of Compound F-like steroids. The basal metabolic rate may actually rise. In Cushing's syndrome, the basal metabolic rate is usually low, although it may be either normal or above normal depending on the degree of inhibition of pituitary thyrotropin secretion and the quantity and type of adrenal corticoids being secreted by the adrenal gland.

VI. EFFECTS OF ADRENAL CORTICAL STIMULATION ON BLOOD

A. *Cytology*: The following effects are due to Compound F-like steroids:

1. *Red Cell Series*: These hormones have been shown to induce a marked reticulocytosis in various diseases(even in pernicious anemia). Prolonged ACTH therapy leads to a general

increase in the number of red cells. However, long standing plastic anemia is not effected. The hematocrit is usually lowered in the initial period of ACTH administration because of water retention and hemodilution. However, following reticulocytosis, the hematocrit may show a gradual rise often increased by the gradual decrease in water retention which occurs on prolonged ACTH therapy.

2. *Leukocytic Series*: ACTH and Compound F-like hormones tend to induce a marked leukocytosis and a shift to the left in most instances. Eosinophiles decrease in the circulating blood, the maximal drop occurring some three to four hours after a single injection of ACTH and culminating in their eventual disappearance on continued administration. Bone marrow production remains the same or actually increases. The ultimate fate of eosinophiles is not known, but indirect evidence suggests that they are destroyed at a more rapid rate than normally. It is on this phenomenon that "The Four-Hour ACTH Test", as devised by Thorn (2c) for estimating adrenal cortical functional reserve is based. A percentage fall in eosinophiles of fifty per cent or more below the pre-injection level and an increase of fifty per cent or more in the uric acid creatinine ratio over the pre-injection ratio usually indicates a satisfactory adrenal cortical response. Under the cortical hormones, Compound F-like, lymphocytes are destroyed. Lysis or lymph nodes in man appears to be relatively limited. The platelet count is inclined to rise. Evidence suggests of a possible relation of the destruction of basophiles to a rise in heparin titre on ACTH. Clinically, however, this has not been borne out; conversely, there appears to be an increased incidence of thromboembolic disease.

B. *Blood Changes*:

1. *Sedimentation rate and plasma fibrinegen.* In diseases reversed by ACTH or Cortisone, and in which these are high, there is a tendency toward a return to normal levels.

2. *Gamma globulin.* Concurrently, or shortly thereafter, there is a trend for this to return to more normal levels under ACTH or Cortisone therapy as in disseminated lupus erythematosis.

3. *Albumin.* In nephrosis and malnutrition, where the serum albumin may be below normal, there is a tendency to return to normal levels on continued ACTH administration.

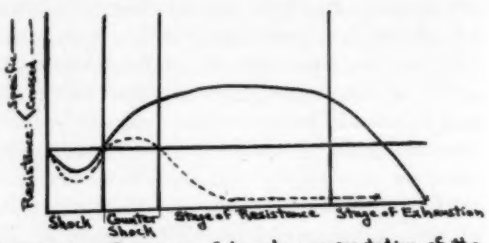

Figure 2.—Alarm Reaction.—Schematic representation of the changes in specific (full line) and crossed (dotted line) resistance during three stages of the General Adaptation Syndrome (Selye).

VII. EFFECT ON ENZYME SYSTEMS

1. *Hyaluronidase*:

Hyaluronidase, or the spread factor, is inhibited in part. This function of ACTH may be an important one by decreasing the shifts of body fluids and materials dissolved in them, and by reducing the intensity of the inflammatory reaction.

2. *Lysozyme*:

It is found in low concentration in the small intestine and in excessive amounts in ulcerative colitis. ACTH greatly decreases the concentration of lysozyme in the latter disease and healing of the ulcerated mucosa proceeds as the intensity of the inflammatory reaction subsides.

3. *Pepsin, Pepsinogen and Urepsin*:

All three show a marked rise during ACTH and Cortisone therapy. Two clinical facts come to mind—the marked rise in appetite found in so many patients, and the deleterious effects in the treatment of gastric ulcers with ACTH in a few human subjects.

4. *Serum Peptidases*:

These rise on ACTH therapy. Since these enzymes enhance the breakdown of protein fragments, their rise may possibly have some significance in connection with the catabolic effect of ACTH and Compound F-like hormones.

5. *Arginases*:

This enzyme is increased on ACTH and may also be related to the anti-anabolic effect of ACTH and cortical steroids.

6. *Histaminases*:

It has been reported that histaminase is increased in both tissue and serum on adrenal cortical stimulation, and this may be one clue to the mechanism of action of the adrenal cortex in hypersensitive states. The characteristic reaction to administered histamine persists unchanged on ACTH. An increased amount of

histidine is found in the urine on ACTH as first reported by Holbrook et al.

Histamine, the biological product of histidine, is formed from it under enzymic or enzymatic action. This is inhibited by Compound F-like hormones (1) and (2). The same hormones also increase urinary excretion of histidine (1) and the destruction of histamine by histaminase (3).

VIII. METABOLIC DEGRADATION PRODUCTS OF ADRENAL CORTICOIDS

A. 11-*Oxysteroids.* If an adequate reserve of adrenal function is present, ACTH produces a marked rise in the excretion of 11oxy and 17-hydroxylike corticoids. A majority of this increased excretion is 17-hydroxycorticosterone, or Compound-F.

B. 17-*ketosteroids.* A portion of the 17-ketosteroids represents androgenic steroid and breakdown products of some of the Compound F-like steroids, such as Cortisone. In the male the testicular secretion provides one-third of the normal value of 17-ketosteroid excretion, whereas in the female the adrenal accounts for most, if not all, of the 17-ketosteroids found in the urine. Following the administration of ACTH there is significant rise in the 17-ketosteroid excretion, due in part to increased formation of adrenal androgens, but also in part to the metabolic breakdown products of Compound F-like steroids such as 17-hydroxycorticosterone and Cortisone. These changes in the 17-ketosteroid excretion are thus a good over-all measure of adrenal cortical activity. It is interesting that an actual decrease in the excretion of this type of compound in patients on medium-sized doses of 17-hydroxycorticosterone or Cortisone, may occur, and this reflects a functional adrenal cortical inhibition.

IX. FUNDAMENTAL AND BROAD PHYSIOLOGICAL PHENOMENA OBSERVED ON ADRENAL CORTICAL STIMULATION.

In general and quite apart from all the above phenomena, there are certain basic phenomena that should be considered for they may be related at the very fundamental tissue cell level to disease processes and their reaction to ACTH administration.

A. ACTH Appears to Render Cells Immune

FIGURE III.—Metabolic and Physiologic Effects of Adrenal Cortical Stimulation

Increased Excretion of N	Sed. Rate, Plasmo Fibrinogen,)Toward Gamma Globulin, Albumin)Normal
Increased Extretion of K+ (Electrocardiographic Changes)	Hyaluronidase Inhibited Lysozyme Decreased
Increased Retention of Na+ & CL− (edema)	Pepsin, Pesinogen, Urepsin Rise Serum Peptidoses, Arginase Rise
Increased Excretion of P+ & Ca+	Histaminase Activity Increased
Glycosuria with or without Hyperglycemia	Histamine Decreases, also Histidine Excretion Increases
Anti-insulin Effect	11-Oxysteroids & 17-Ketosteroids Increased in the Urine
(GSH Antagonizes Diabetogenic Glutathione Decreases Effect of ACTH)	Cells Rendered Immune to Toxic Agents (Bacteria, Antigens, Chemicals)
Anti-anabolic Effect (CHO-Sparing Effect)	Inflammatory Reaction Inhibited
Creatinine Excretion Increased	Fibroblastic Proliferation Inhibited
Uric Acid Excretion Increased	Fever and Pain Inhibited
Increased Production, Mobilization and Utilization of Fat	Wound Healing Delayed BP Normal or Increased
BMR Decreased	Euphoria to Psychosis
Giant Lipo-protein Molecules Increased	Androgenic Effects (acne, hirsutism, amenorrhea, thinning of hair)
Reticulocytosis, Leukogtosis (with Shift to Left)	In Males—Importence & Sex Drive
Circulating Eosinophiles Decrease (Thorn Test)	Adrenal Atrophy or Hypertrophy
Lymphocytopenia, Basophilopenia, Platelets Increased	Miscellaneous—Moon Face Buffalo Hump, etc. . . .

to a Wide Variety of Known Toxic Agents. For example:

1. *Bacteria.* A patient may have peritonitis or a pneumococcal septicemia without fever, or any clinical evidence of infection. The pneumonia may resolve rapidly.

2. *Antigens.* Highly sensitive individuals may be exposed to specific antigens or drugs while under ACTH administration with no deleterious effect. This may be related to the possible mechanism involved in effecting a decrease in tissue histamine as just described.

3. *Chemicals.* A patient sensitive to iodine, aminopterin, or mustard gas will show no idiosyncrasies toward these chemicals while on ACTH.

B. *Inhibition of the Acute Inflammatory Reaction*:

ACTH will inhibit or block acute inflammatory reactions from almost any cause. Thus, the peritoneal cavity may be grossly contaminated by gastric or fecal material, yet there will be little to no inflammatory reaction in the peritoneum. In the near future it will have to be decided just what constitutes a beneficial inflammatory response and doses of ACTH and Cortisone will have to be adjusted accordingly for optimum benefit.

C. *Inhibition of Excessive or Prolonged Fibroblastic Proliferation*:

ACTH inhibits or blocks excess fibroblastic proliferation almost regardless of cause. This may well be one of the basic mechanisms involved in a number of chronic proliferative diseases, such as rheumatoid arthritis.

D. *Inhibition of Fever*:

Adrenal cortical stimulation appears to inhibit fever from almost any cause.

E. *Inhibition of Pain*:

Whatever the cause, pain is inhibited or blocked by the administration of ACTH.

A patient on prolonged ACTH administration suddenly developed an unexplained tachycardia for several days, and no other sginicant signs or symptoms. ACTH was stopped and in a matter of hours he began to complain of substernal pain radiating to the left shoulder, and developed fever, leukocytosis, etc., the typical clinical picture of coronary occlusion.

FIGURE IV

Probable Sites of Action of Adrenal Steroids in Decreasing Tissue Histaminase

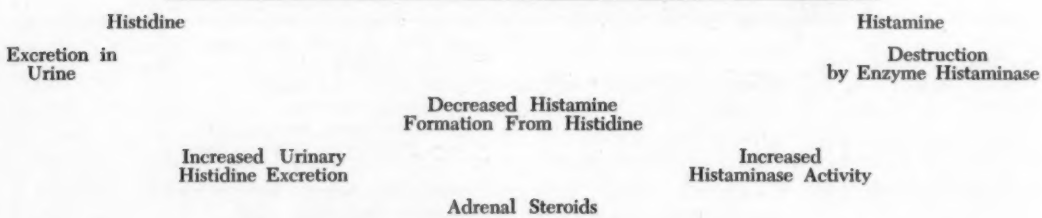

FIGURE V.—The New England Journal List of the Preliminary Grouping of Disease on the Basis of the Response to ACTH and Cortisone Therapy

Diseases in Which Drugs Are Most Useful	Diseases In Which Drugs May Be Useful	Diseases In Which Drugs Are of Questionable Value	Diseases In Which Drugs Are Of No Value	Diseases In Which Drugs May Be Detrimental
Addison's Disease	Rheumatoid Arthritis	Mental Disease	Herpes Simplex	
(Cortisone only)	Psoriasis	Multiple Sclerosis	Herpes Zoster and	Diabetes Mellitus
Panhypopituitarism	Disseminated Lupus	Pemphigus	Varicella	Cushing's Syndrome
Functional Adreno-Cortical	Erythematosis	Scleroderma	Poliomyelitis	Hypertension (ACTH)
Insufficiency	Dermatomyositis	Myasthenia Gravis	Progressive Muscular	Congestive Heart
Functional Hypopituitarism	Periarteritis Nodosa	Osteoarthritis	Dystrophy	Failure
	Acquired Hemolytic	Paget's Disease	Progressive Muscular	Osteoporosis
Anorexia Nervosa	Jaundice	Tuberculosis	Atrophy	Acne
Idiopathic Hypoglycemia	Vasomotor Rhinitis	Pneumonia	Cystic Fibrosis of	Hirsutism
	Urticaria	Anoxia	Pancreas	
Acute Rheumatic Fever	Multiple Myeloma	Pernicious Anemia	Peptic Ulcer	
Acute Gouty Arthritis	Lymphoma	Liver Disease	Sarcoidosis	
Status Asthmaticus	Leukemia	Thyrotoxicosis		
Serum Sickness	Nephrotic Syndrome	Malingnant Exophthalmos		
Exfoliative Dermatitis	Ulcerative Colitis	Glomerulonephritis		
Loeffler's Syndrome	Regional Enteritis	Cancer		
Acute Inflammatory	Pulmonary Berylosis	Hypertension (Cortisone)		
Disease of Eye				

F. *Adrenal Cortical Stimulation and Central Nervous System Physiology*:

Regardless of the disease in question, most patients receiving ACTH are inclined to develop a sense of well-being and a sense of mental activity bordering on euphoria. When relief is obtained from a chronic, painful, debilitating disease, the sense of well-being may be a natural consequence. However, electro-encephalographis recordings on patients on ACTH administration reveal that the alpha waves are of both larger magnitude and shorter intervals, suggesting that there is an effect upon the physiology of the individual neurones. Therefore, the patient on high doses of ACTH should be carefully observed from a psychiatric viewpoint since overstimulation may bring subclinical psychoses to the clinical level in rare cases.

G. *Additionals*

Two unpleasant complications of prolonged therapy with ACTH or Cortisone have been clinically noticed by local observers which, heretofore, have not been reported in the literature. There is what appears to be an increased incidence of thromboembolic accidents and second the occurrence of pathological fractures from minimal trauma, no doubt a result of the osteoporosis which develops on prolonged administration of these substances.

X. EFFECT ON DISEASES:

Time does not permit a detailed account of the great number of diseases studied which either respond very dramatically or at least show some improvement with either ACTH or Cortisone therapy. I will merely mention certain diseases that have responded exceedingly well, and others that have responded enough to warrant careful continuation of studies. Figure V. shows examples of diseases treated using the New England Journal List as an outline. In addition to rheumatoid arthritis, acute rheumatic fever, chorea, disseminated lupus erythematosis periarteritis nodosa, dermatomyositis, and scleroderma are included, plus many varied diseases which appear to have no relation, such as ulverative colitis, malignant exophthalmos, Grave's thryotoxicosis, spontaneous hypoglycemia, gout, acute nephritis and nephrosis, and malignant lymphomas have been affected importantly, as have various types of leukemia.

Early silicosis and beryllium granulomatosis (13) respond to ACTH. Silicosis, as you know, is a disease in which one sees tremendous fibroblastic proliferation as a result of the silica. We do not see the silica in the X-ray, but we see much fibroblastic proliferation. If Cortisone stops fibroblastic proliferation, then we can see some possibility for explaining this result. In myasthenia gravis, interesting things have been observed with ACTH which require much more study. Certain diseases, like primary atypical pneumonia and acute hepatitis, have responded dramatically to these compounds. Findland (14) has found some very important effects in pneumococcal pneumonia, as mentioned earlier.

Recent reports indicate that in exudative pulmonary tuberculosis, the exudation disappears very rapidly. Keep in mind that one must be very careful with respect to tuberculosis, since it must be realized that there is an inhibitory effect upon fibroblasts. These hormones could conceivably prevent or break down a cellular barrier and allow a spread of active tuberculosis.

Iritis, uveitis, interstitial keratitis, and other ophthalmological conditions respond to these materials, where other treatments have failed.

In major surgery, the adrenal hormones of the "11-17-oxy" type are of vital importance in the reaction of the organism against stress. Hence, clinically it would be of great importance to be able to reveal the presence of these hormones in adequate amounts. Thorn (2d) and workers have studied this problem. To test adrenal cortical function, two methods were used as indices, (1) The Four-Hour ACTH Test, and (2) The Epinephrine Test. The administration of ACTH or Epinephrine both lead to an eosinopenia. A fall of 50% or more four hours after the injection of either of these compounds is considered a normal response. The two tests differ in the mechanism of the production of this response; ACTH by directly stimulating the adrenal cortex, and Epinephrine by stimulating the pituitary-adrenal mechanism (or the hypothalamic-pituitary-adrenal mechanism).

In the presence of normal adrenal cortical activity, there is an almost complete disappearance of circulating eosinophiles during the first 24-48 hours after a major operation (counter-shock phase of The Alarm Reaction). This is in itself evidence of increased cortical activity. Conversely, the finding of a normal or high eosinophile level during the first 24-48 hours after an operation suggests adrenal cortical insufficiency, in the absence of allergy. Approximately 72 hours post operatively, there is usually a sharp

rise of the eosinophile level, apparently indicating a return of adrenal cortical activity to a more normal plane. The use of The ACTH Test before surgery is a good index of the capacity of the adrenal cortex to excrete 11-oxysteroids and furnishes a good means of pre-operative prognosis.

It is now apparent that ACTH given intravenously will be a valuable adjunct to the therapy of acute traumatic shock, severe burns, long shocking operations, poor surgical risks, and even in the shock produced by acute blood loss.

XI. SIGNS AND SYMPTOMS OF OVER-STIMULATION

Briefly, let us summarize the clinical evidence of over-stimulation:

1. Edema. A rapid, unusual weight gain may be an early indication of impending edema. This can be minimized by a low salt, high potassium intake, decreasing or omitting doses, and diuretics. Recently, certain resins given orally affecting ion transfers in the gastro-intestinal tract are said to aid in the excretion of sodium.

2. *Weight loss or nitrogen loss.* Usually this effect is minimized by a high protein diet or by the administration of 25 mg. of testosterone daily by mouth. Again, recently, an androgen has been found that has the anabolic effects of testosterone but little to none of the masculinizing properties of the latter.

3. *Hyperglycomia and glycosuria.* This is seldom a problem except in those patients with a familial background. Usually it is controlled either by lowering the dose or administering insulin.

4. *Hypertension.* Daily routine blood pressure readings should be done. Hypertension may be transitory during the period of electrolyte and water retention. It may be controlled by decreasing the dose. If it persists ACTH should be discontinued. Persistent hypertension may reflect parenchymatous renal disease, as in some cases of disseminated lupus erythematosis.

5. *Muscle weakness, fatique, exhaustion or parasthesias.* These may be a reflection of potassium deficiency and blood potassium levels and electrocardiograms should be obtained. In most cases these signs and symptoms, if due to potassium deficiency, can be corrected by increasing the potassium intake and lowering the dose of ACTH. Suppresion of the adrenal cortex after prolonged Cortisone administration has been incriminated.

6. *Disturbed psyche.* The patient should be observed for exaggerated euphoria or nervousness and pronounced insomnia or depression. If these occur ACTH should be reduced and proper sedatives given as indicated Should psychotic changes become severe or persist, ACTH should be stopped, sedation and possibly other measures instituted as indicated.

7. *Miscellaneous effects.* Rounding of the face (moon-face), the fat pad between the scapulae (buffalo hump), and other distributions of fat peculiar to Cushing's syndrome are seen, even when there has been no significant increase in weight (edema). This has been attributed to redeposition of fat.

Thinning of the skin, reddish or purplish striations, acne, and hirsutism as seen in Cushing's syndrome have been observed both in males and females when ACTH is given in large doses. Amenorrhea may be hormonally induced or maintained. This is more apt to occur in adolescent girls. In males a diminution in sex drive has been observed in some cases. Impotence is a common occurrence in men with Cushing's syndrome.

XII. FUNCTIONAL DEPRESSION OF THE ADRENAL CORTICES

The evidence reported by Sprague (15) and co-workers is strongly suggestive of depression of some functions of the adrenal cortex by Cortisone. After withdrawal of Cortisone, asthenia and impairment of the eosinophilic response to ACTH occur. Also, the urinary excretion of 17-ketosteroids is decreased during administration and after withdrawal of Cortisone. From a practical standpoint, a patient who had recently received Cortisone, the possibility should be borne in mind that the function of the adrenal cortex may be so depressed that it may be inadequate under conditions of stress, such as trauma, infection, etc. The adrenal cortex may be refactory to the administration of ACTH for a variable period after withdrawal of Cortisone.

XIII. DOSAGE AND METHODS OF ADMINISTRATION

In view of the fact that adrenal cortical stimulation affects so many important metabolic and physiologic processes in the body, it is essential to become fully familiar with the changes that may occur on adrenal cortical stimulation with ACTH. Likewise, dosage schedule should

be considered in the light of the alterations that may occur.

Since the adrenal glands of different individuals vary considerably in their sensitivity to stimulation by ACTH, there is no constant, specific, uniform dose that is effective in all individuals. A few individuals need as little as 5 mgm. of ACTH four times a day, while others require as much as 50 mgm. four times a day. This relative effectiveness of ACTH which is also true for Cortisone, may be related to the functional state of the adrenal cortex at that moment. In complete adrenal insufficiency ACTH will produce no effects, whereas, in a functionally large and sensitive adrenal cortex a given dose of ACTH will produce a maximal effect. Cortisone, on the other hand, by inhibiting both endogenous ACTH and the adrenal cortex directly to some extent, will lose a large portion of its potential effectiveness.

In general, however, 25 mgm. of ACTH four times a day is sufficient to cause definite metabolic alterations, therefore, unless a clinical effect is not obtained smaller doses should be used which cause relatively slight or even non-detectable metabolic changes and are still therapeutically effective in a substantial number of various disease syndromes.

It is desirable to start the patient on a 10 to 12.5 mgm. of ACTH four times a day and to hold the patient on this dose level for several days to ascertain if a clinical effect can be obtained. If not, the dose is gradually increased, observing the patient for several days on each dose increment until a clinical effect is obtained keeping in mind the metabolic alterations to be avoided. Each dose is given at six hour intervals in view of the evidence that has accumulated that the clinical and physiological effect of ACTH is largely worn off in this period of time. For prolonged therapy it is desirable to maintain the patient on the smallest clinically effective dose. The administration of ACTH should never be stopped suddenly at a high dosage level, because there is definite evidence that there is a period of adrenal cortical hypofunction (exogenous ACTH may depress production of endogenous ACTH through the increased titre of the adrenal steroids) anywhere from two to five days after cessation of therapy. Tapering off the dose gradually will allow the patient's own pituitary to take over the secretion of endogenous ACTH for his own adrenal cortical stimulation.

Unresponsiveness to ACTH may be due to two general causes: to a relatively poor adrenal cortical reserve, or to a possible occurrence of antibodies against an ACTH preparation. The latter cause is rare and should be thought of when a second course of therapy is begun and a therapeutic effect is not obtained. In such cases ACTH prepared from another species should be used.

As you know, ACTH is a protein substance, and as such it cannot be given orally because of the destructive action of the gastro-intestinal enzymes. It has been prepared in three forms for parenteral use. The preparation now in common use is a dry powder which is extracted from the pituitary glands of domestic food animals and is put in solution by dissolving it in sterile saline. This form is administered intramuscularly and, as already mentioned, its effect is over within six hours. The main objection to this preparation is the necessity of the frequent daily injections. Two longer acting preparations are still in the investigative stage. One is ACTH in propylene glycol which can be given subcutaneously in a single daily dose. Even longer intervals may be effective. The other is ACTH in an oily vehicle, which is injected intramuscularly.

Because of the possibility that some of the ACTH injected intramuscularly may be destroyed by the peptidases in muscle, it may be that the subcutaneous route will be the most desirable although somewhat more painful. The aqueous preparation has recently found a new use in surgery. Small doses of 10 to 25 mgm. may be given intravenously over a period of hours in an infusion to patients preoperatively, during the operation, and post-operatively as the indication arises. Surgical procedures are tolerated extraordinarily well and operations that would otherwise not be attempted can be performed.

Cortisone, on the other hand, is prepared for intramuscular injection as a suspension in saline solution. It is being synthesized from bile acids. As with ACTH, the object of treatment is to obtain the maximum effect with the minimum dosage. The recommended dosage for the initial period in rheumatoid arthritis is as follows:

100 mgm. every 8 hours for 3 doses, then
100 mgm. every 12 hours for 2 doses, then

100 mgm. every 24 hours for 7 to 14 days or less.

When the desired response appears, the dosage is lowered by 10 to 15 mgm. at two to three day intervals until the total daily dose is 50 mgm. This may be changed to 100 mgm. every other day. If any significant relapse occurs, revert immediately to the 100 mgm per day dose until the desired response again appears before lowering the dosage. Dosages in other diseases appear to be comparable to that outlined for rheumatoid arthritis.

Cortisone may be administered orally. However, because of the rapid absorption from the gastro-intestinal tract, the total daily dose is given in equally divided doses every six hours. The maximum clinical and physiological effect of Cortisone by this route appears to reach its peak in three to four hours and is almost completely dissipated in six hours.

XIV. THEORIES CONCERNING THE MACHANISMS OF ACTION.

What is the endogenous mechanism that fires off the pituitary gland to secrete ACTH in response to a stress situation? The most attractive theory to date is that formulated on the basis of Harris's (16) work on the rabbit and Hume's (17) work on the dog (See Figure VI). The phenomenon of activating the pituitary through a peripheral sensory stimulus has been well recognized in relation to the production of gonadotropic hormones. By stimulating the cervix in rabbits, Harris was able to induce pseudopregnancy and in the case of ovulation, it is known that rabbits will ovulate only after copulation. As an extension of this prior knowledge, Hume has shown that:

1. Following stress, an intact hypothalamus is necessary for the increased release of ACTH;

2. This hypothalamic control of the pituitary seems to be on a hormonal basis, and

3. Following operative trauma, the release by the pituitary of an increased amount of ACTH is dependent upon an intact nervous connection between the injured area and the brain (even in the completely sympathectomized animal). An interesting point that confirms this is the somewhat delayed eosinophilic response, with respect to speed, in the patient with spinal anesthesia over the patient with general anesthesia. This suggests that the normal adrenal cortical stimulation may not occur until the spinal anesthesia wears off. Preliminary

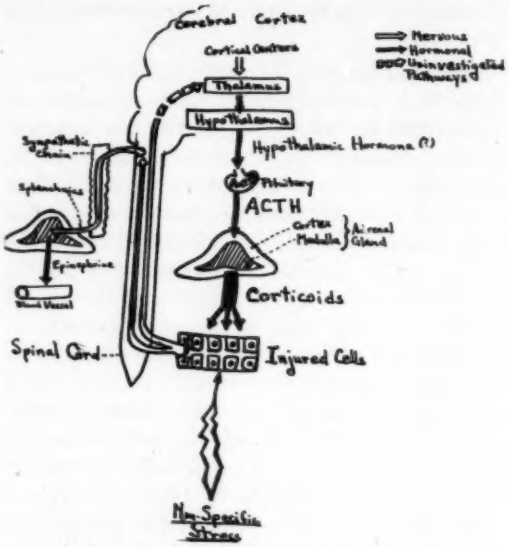

Figure VI: Diagramatic Representation of the Pathways Involved in the Increased Secretion of ACTH by the Anterior Pituitary Gland.

work with beef hypothalamic extracts seems to indicate that some specific substance is formed in the hypothalamus which will stimulate the production of ACTH from the anterior pituitary gland.

This mechanism of ACTH production may be supplemented by other pathways. For example, a reduction of arterial oxygen saturation to 70-75% was followed by a fall in the circulating cosinophiles of about 40%. This stress may not involve an increased production of adrenalin or the hypothalamic centers, so that it might bring on the secretion of ACTH through increased peripheral utilization of the adrenal cortical hormones.

Toxic metabolic products produced by injured tissues have also been suspected of possibly exerting an effect on the anterior pituitary gland to increase the secretion of ACTH.

The ultimate goal of clinical research is to discover the basic processes that occur at the "tissue level." Are these processes of an enzymatic nature? Is there a decrease in cell permeability since they do not react to known toxic agents? The truth of the matter is that no one knows for sure.

XV. SUMMARY

In summary, suffice it to say that a new era has been opened up which will require a tremendous amount of imagination and work to

arrive at the final answers concerning the true etiology and therapeutics of a large number of diseases that afflict the human race.

I would like to extend my thanks to Dr. C. A. L. Stephens, Jr., and W. Kirby West for their valuable assistance in the preparation of this paper.

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PHOENIX CLINICAL CLUB MASSACHUSETTS GENERAL HOSPITAL CASE NO. 28422

The Case History in this discussion is selected from the Case Records of the Massachusetts General Hospital, and reprinted from the New England Journal of Medicine. The discussant under Differential Diagnosis is a member of the staff of the Massachusetts General Hospital. The other discussants are members of the Phoenix Clinical Club.

A thirty-four-year-old woman was referred to the hospital because of chest pain.

The patient had been in good health and had been active until about one month prior to admission, when she developed an upper respiratory infection with coryza, slight transient sore throat and malaise. Two or three days afterward, late one afternoon, she suddenly experienced a severe sharp, steady, nonradiating pain in the anterior chest just to the right of the sternum at the level of the fourth rib. The pain was aggravated by coughing and respirations, by lying down on the right side and by downward traction on the right arm. The pain persisted, with sharp exacerbations on coughing, for one week, during which time the patient remained in bed. She was afebrile and there were no sputum, night sweats, hemoptysis, dyspnea, palpitation and orthopnea at that time. On the third day after the onset, her physician made a diagnosis of pleurisy and accordingly strapped the chest, with some relief. Soon after this, she resumed ambulatory activities, but had several more attacks of the same pain, milder in degree and lasting approximately one hour. Because of the persistent pain, an x-ray film of the chest was taken two weeks before entry. This showed "congestion of the right lung." Since the x-ray study, the patient had had no further pain or other symptoms. She had taken no cognizance of her weight variations, but her clothes remained well fitted.

The family history and past history were noncontributory, except that she had occasionally noted ankle swelling in the evening.

Physical examination revealed a well-developed and well-nourished woman in no acute distress. Examination of the heart and lungs was negative. There was slight tenderness on pressure over the spine at the level of the sixth dorsal vertebra. The abdominal examination was not remarkable.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 99.8°F., the pulse 80, and the respirations 20.

The examination of the blood revealed a red-cell count of 4,770,000 with a hemoglobin of 90 per cent, and a white-cell count of 10,100 with 74 per cent polymorphonuclears. The urine examination was negative, as was the blood Hinton test.

An x-ray film of the chest demonstrated an 8 x 5 x 6.5 cm. slightly lobulated, homogeneous mass in the right cardiophrenic angle. Its anterior surface touched the anterior chest wall, and its lower pole reached to the diaphragm. No calcium was seen within it. The heart and lungs were not remarkable. The diaphragm was normal in position. An x-ray film of the dorsal spine showed no evidence of disease.

Fluoroscopy confirmed the findings of a lobulated tumor in the anterior mediastinum. The fifth day after admission, the patient was operated on.

HOWELL RANDOLPH, M.D.

This protocol contains several rather glaring inconsistancies at which, as practical clinicians, we have learned to look askance. For example there is a careful description of a pain at the level of the right fourth rib, also of a pain at the sixth cervical spine. There is no sputum, but the pain is "aggravated by coughing"; there has been "swelling of the ankles" but they found the cardio-renal system negative in a young woman without cardiac history or other findings to explain it. These statements must be attributed either to an over-zealous resident or to a neurotic patient.

What about the acute respiratory infection at onset? Did that have anything to do with the pulmonary pathology? I don't believe it likely. That infection merely served to call attention to the chest where it settled in that right lung field and was found on the first x-ray. Did the acute shadow obscure the rounded shadow on that first film, or did the "lobulated homogeneous mass" develop following this acute infection? Suppose we follow the latter possibility first. We come up with localized empyema, localized abscess or fungus disease, cystic structures such as ecchinococcus cyst, torula, hardly tuberculoma in such a short time; but any of these conditions could have been dormant and reac-

tivated by the acute infection.

The "phantom tumor" of the chest is an intriguing condition which may be present one day, disappear three or four days later, and then reappear. Its frequency may be greater than we realize in view of the fact that these patients have not had the frequent routine fluorescopic observation and chest x-ray that would be needed for its detection. The shadows may be easily confused with those of malignancy or other conditions, but are interlobar in distribution. This condition is the result of cardiac decompensation, and the shadow is produced by a localized pleural effusion. Mercuhydrin produces a dramatic disappearance of the lesion, and the bringing about of cardiac compensation may cure it permanently.

In the case under discussion the final description of the mass on the admission X-ray seems now quite different than on the previous film. A definite circumscribed shadow is described, with the homogeneous character of a solid or fluid consistency. It is spoken of as lobulated, and by this I suppose is meant also that its outlines are well and sharply delineated. There seem to be relatively few things that fit this picture. Pulmonary cysts of long standing which become infected may cause temporary increase in symptoms, with pleurisy and pain fitting this patient's symptoms and this X-ray picture. These cysts are endothelial lined or they may have evolved from respiratory epithelial lined spaces. They may exist within the lung parenchyma, most frequently in the anterior parahilar position, in the dormant state for years. They may have been started by an original infection followed by blocking of the drainage, with a later sterilization of the cavity through natural immunity processes.

The pericardial celomic cyst has a rather similar origin and evolution. Its origin adjacent to the pericardium gives it the name, but it also may be from lung structures. Cystic developments from the esophagus may present in the right side at this low level. The tumor may contain a light brownish material from which colon bacilli may be cultured. Its X-ray appearance is as a large, round circular tumor. It is more posterior than the tumor of our patient.

The paraffinoma is a tumor found in any part of the lung, even the upper lobes, surprisingly enough. It more frequently produces diffuse pneumonitis shadows, but there may be a circumscribed, rounded and nodular lesion, and this patient's signs could be well explained by such a lesion. The history of mineral oil inhalation has been withheld, however.

Many other lesions of chronic nature might be mentioned such as neurofibroma, hamartoma, bronchial adenoma and arteriovenous aneurysm. A most common lesion is the dermoid cyst, and this location is perhaps the most frequent site of this tumor. On the basis of the most common and likely lesion in this location, my diagnosis is pleuro pericardial cyst, either endothelial lined or with respiratory epithelial lining. Second Diagnosis, Dermoid.

DIFFERENTIAL DIAGNOSIS

Dr. Jacob Lerman: Perhaps we had better look at the x-ray films first.

Dr. George W. Holmes: The shadow that you see in the left lung is not important. Here is the shadow under consideration. Two oblique and a lateral view were taken. I should place the lesion in the anterior mediastinum. The shadow is quite homogeneous, sharply defined and lobulated. That is, it appears to be a solid tumor. So far as we can tell, it is in contact with the anterior chest wall.

Dr. Lerman: Could it be encapsulated fluid?

Dr. Holmes: No, because of the location. We practically never see fluid in that area. The heart and lungs are apparently normal.

Dr. Lerman: The differential diagnosis here centers about the types of mediastinal tumors. I shall first discuss lesions arising outside the mediastinum that eventually lodge in the mediastinum, and second, lesions arising in the mediastinum itself.

One should consider diaphragmatic hernia. Only a very unusual one lodges in the right chest. One might suppose that the hernia went through the anterior attachment of the diaphragm. This type, however, is extremely rare, and I mention it only in passing.

Intrathoracic goiter has to be considered, but it must be of an extremely unusual type to fit this case. Intrathoracic goiters in this region are rare; most occur in the upper mediastinum. Certainly the shape of this tumor is unusual for intrathoracic goiter. Usually, it is a single round nodule and not a lobulated mass that plunges down into the chest to rest on the diaphragm, and it lodges posteriorly rather than anteriorly.

I do not believe this is an aneurysm, because

no definite connection between the mass and the aorta was visualized. The presence of pulsations is not mentioned, although they are not absolutely necessary for diagnosis. Moreover, there is no history or physical findings of syphilis, and the Hinton test was negative. I am not at all concerned about aneurysm.

In considering the diagnosis of mediastinal tumor, one must first settle the question whether the mass is benign or malignant. I think we can state definitely that this mass is not a malignant tumor. The patient was symptomless, except for inconstant pain; there was no evidence of invasion of surrounding structures and organs, and there was no toxemia. Consequently, we can rule out a malignant type of tumor.

Although I doubt that I can make a better diagnosis than jusst benign mediastinal tumor, I must consider the several varieties. The description of the tumor, the short duration of pain and the unknown duration of the tumor are consistent with dermoid, which also is the most common statisticaly. On the other hand, several cases with similar findings that have been discussed at these meetings were found to have had either a neurofibroma, chondroma, lipoma or cyst. We saw one mediastinal tumor here a year ago that gave similar symptoms and had a similar appearance in the x-ray films, which the pathologist called hemangioma. One should mention thymoma as a possibility. It must have extended from its origin in the thymus down to this region. I have no way of confirming this diagnosis.

As Dr. Holmes said, it is unusual to find encapsulated fluid in this location, although the history of pleurisy a month before admission raises the question of fluid in the pleural space. Moreover, lobulation of the mass argues strongly against encapsulated fluid. Consequently, I shall not consider it further.

In conclusion, I believe this is a benign mediastinal tumor, either neurofibroma or dermoid.

Dr. William B. Breed: I wonder if enough stress has been laid on the fact that this whole episode was ushered in by an acute respiratory infection. That may be of some importance, and the mass may still be encapsulated pus. Perhaps this point should be stressed just a little more than it was in the discussion.

Dr. Lerman: Dr. Churchill has emphasized many times that the symptoms of these patients have been influenced by his opinion. Many patients come in with bizarre complaints, and a tumor is found incidentally. I think the onset of the respiratory infection served to focus attention on something in the chest.

Dr. Ralph Adams: Did this mass move with swallowing?

Dr. Tracy B. Mallory: I do not believe so.

Dr. Edward D. Churchill: This is all a guessing game, for it is very difficult to arrive at any preoperative diagnosis except mediastinal tumor, benign or malignant. There are two or three additional diagnoses that occurred to me as I listened to the discussion. I should think of a hernia through one of the apertures of the diaphragm and should have advised a barium enema. There is another lesion that we have come to recognize particularly along the right border of the pericardium,—namely, a thinwalled cyst containing clear fluid. These cysts are comparable to the cystic hygromas that are found in the neck. Perhaps Dr. Mallory can say whether they are of lymphatic origin or of endothelial origin from adjacent serous cavities.

I wish Dr. Holmes would take a stand on the question whether this particular patient should have received a diagnostic dosage of radiation therapy to rule out lymphoma or another radiosensitive tumor before operation.

Dr. Holmes: As a general rule, I think the diagnosis should be established, whenever possible, before we subject a patient to x-ray therapy. But it depends largely on the severity of the operative procedure planned. If it is to be a simple operation, probably x-ray therapy should not be given; on the other hand, if it is a dangerous operation, I should advise giving a small dose.

Dr. Churchill: Will you feel badly if some day I enucleate such a tumor and it turns out to be lymphosarcoma or lymphoma?

Dr. Holmes: No.

Dr. Churchill: Will you, Dr. Mallory?

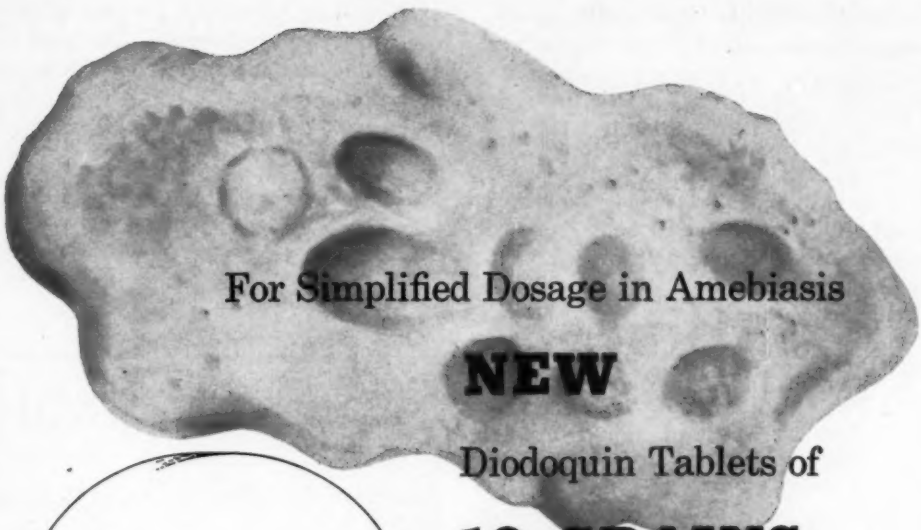
Dr. Mallory: No. It might be good treatment. I think when an isolated tumor is resectable it is wise to remove it, because very long cures often follow the procedure.

CLINICAL DIAGNOSIS

Mediastinal tumor (? dermoid cyst, ? neurofibroma, ? lymphoblastoma).

DR. LERMAN'S DIAGNOSIS

Benign mediastinal tumor (neurofibroma or dermoid).



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SEARLE RESEARCH IN THE SERVICE OF MEDICINE

ANATOMICAL DIAGNOSIS

Pleuropericardial cyst.

PATHOLOGICAL DISCUSSION

Dr. Mallory: This patient did turn out to have a cyst filled with perfectly clear fluid. The cyst has a fibrous wall with an occasional smooth muscle fiber in it, looking essentially like pleura. It is lined with a low cuboidal epithelium that occasionally seems multilayered, which is probably due to tangential sectioning; it seems likely that the epithelium lining was only a single layer thick. So far as the appearance of the cells is concerned, they colud either be mesothelial, such as those that line the pleura, or endothelial, which one would find lining a lymphatic vessel. I do not believe I can answer Dr. Churchill's question. I have a little preference for the theory that this sac is made up of pleural or pericardial tissue than that it represents a cystic lymphangiomatous tumor, such as a cystic hygroma of the neck.

Dr. Holmes: Perhaps we should have observed it on inspiration and expiration to see if there was a change in shape, which one might expect if it had a thin wall and contained fluid.

Dr. Mallory: Should this tumor perhaps have been needled before operation?

Dr. Churchill: I do not think so.

Dr. Mallory: If it had been, could you have made the diagnosis?

Dr. Churchill: Probably, but we should not have known what to do in the way of treatment. I do not believe it is without danger to put a needle in so close to the pericardium. There is always a possibility that one is dealing with an aneurysm of the auricle.

Dermoids are likely to be a bit higher on the right and a little closer to the lung root. When a tumor lies in the cardiophrenic angle, a simple cyst must be seriously considered.

Dr. Mallory: Sometimes, there is a rather unusually large amount of fat tissue in that location. Does that ever cause clinical confusion in case of this sort?

Dr. Churchill: I do not recall having been misled by a fat pad.

Dr. Allen G. Brailey: The patient would have been perfectly well if left alone?

Dr. Churchill: I think she would have.

Dr. Mallory: We have no idea of the rate with which these cysts grow. It is quite doubtful that this had anything to do with the symptoms.

Dr. Churchill: I also think that it is very doubtful. One must remember, however, that the presence of an x-ray shadow of this type is sufficient reason for employment rejection by many large industrial plants and, of course, by the armed forces. She can now join the WAACs or WAVES.

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The Editor sincerely solicits contributions of scientific articles for publication in ARIZONA MEDICINE. All such contributions are greatly appreciated. All will be given equal consideration.

Certain general rules must be followed, however, and the Editor therefore respectfully submits the following suggestions to authors and contributors:

1. Follow the general rules of good English, especially with regard to construction, diction, spelling, and punctuation.

2. Be guided by the general rules of medical writing as followed by the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. (See MEDICAL WRITING by Morris Fishbein.)

3. Be brief, even while being thorough and complete. Avoid unnecessary words. Try to limit the article to 1500 words.

4. Read and re-read the manuscript several times to correct it, especially for spelling and punctuation.

5. Submit manuscript typewritten and double-spaced.

6. Articles for publication should have been read before a controversial body, e.g., a hospital staff meeting, or a county medical society meeting.

The Editor is always ready, willing, and happy to help in any way possible.

Editorial

L. DONALD LAU
"MR. BLUE CROSS"

In recent years our attention has been directed to such national figures as Bing Crosby, referred to as "Mr. Music"; Joe DiMaggio as "Mr. Baseball"; Senator Robert Taft as "Mr. Republican"; and our own Jacque Mercer as "Miss America."

Within our great state there are also a number of Arizonans, both native and adopted, who have equally distinguished themselves by their singular accomplishments. These talented people, too, have justly earned for themselves the similar titles of "Mr. Music' (Robert Lawrence); "Mr. Baseball" (Del Webb); "Mr. Republican" (Governor Howard Pyle), to mention but a few. Your Editor wishes to add another name to this list—a person whose outstanding accomplishments in his chosen field have rightfully earned for him the title of "Mr. Blue Cross."

As executive director of Arizona Blue Cross-Blue Shield, L. Donald Lau has contributed much in six short years to the economics of the medical profession, the financial stability of our hospitals and the health care of our communities throughout Arizona. Today, Blue Cross' membership consisting of one out of every six and Blue Shield's, one out of every nine persons presently living in the State, stands as mute but effective testimony of the sound, progressive administration and the far-reaching influence of our own hospital and doctors' voluntary, prepayment hospitalization and surgical care plans. Assuming the guardianship of these "adopted children" has been no picnic for Don Lau.

Let's go back a bit.

In 1939, a period when Arizonans were still feeling the depression, William J. Wasson, a present Blue Cross Board member and an active, civic-minded Phoenician, realizing the people, as well as the hospitals of this State were in need of a plan whereby hospital bills could be met through reasonable prepayment methods, conceived the idea (and subsequently was one of its incorporators) of organizing the Associated Hospital Service of Arizona. This Association was patterned after but not approved as a member of the national Blue Cross plans. Operating in a "borrowed" corner of Wasson's office, it started with three hospitals and a limited Service Contract of Benefits. Mr. Wasson also contributed much of his time and effort to organizing and directing the new enterprise. The plan grew, but soon the rumblings of World War II were heard and as a consequence, the plan was put in "moth balls" for the duration.

In the latter part of August 1944, Don Lau had occasion to visit the Valley of the Sun, and like many others before and after him, decided to stay. By mere coincidence he learned of the then dormant Hospital Service Association and promptly made contact. Conferences followed, resulting in Don's being offered the position as director of the plan. Before accepting however, he first decided to make a survey of the leading industries and business firms throughout the State to ascertain whether a Blue Cross plan would receive as favorable reception here as he had, through experience, observed in his native State of Pennsylvania. On his tour throughout Arizona, Don acquired sufficient evidence of interest to write C. Rufus Rorem, then director of the Blue Cross Commission, stating that he would accept the position as executive director of the Associated Hospital Service of Arizona on condition that Blue Cross approval would be secured.

William S. McNary, then executive director of the Colorado Blue Cross plan and also a Commissioner, came to Phoenix on September 11,

1944, to assist L.D.L. in the reorganization process, necessary for eligibility for Blue Cross approval. Conferences with hospital administrators, medical doctors and laymen followed and much midnight oil was spent on the development of new contract benefits, rate structures, corporate policy changes, etc., to meet approval standards. During this time, the two men would meet at their spacious but rather public headquarters—a bench under a certain palm tree in Encanto Park. Finally the mold was complete and McNary submitted his report to the Commission. On October 5th, just six weeks from the time L. Donald Lau took over, the Association received official notification by the Blue Cross Commission in Chicago that it was formally approved as a Blue Cross Plan.

Again, the first official Blue Cross office was a borrowed space in Wasson's office, consisting of two borrowed desks, one borrowed typewriter, a borrowed waste-paper basket, telephone stand one old but usable file. Group enrollment was opened to the public on November 15, 1944 and a little over 200 of the old association memberships were converted to the new Blue Cross contract. The staff consisted of L.D.L. and Miss Alice Murphy. Together, they functioned as the enrollment, service, case, accounting, research, purchasing, personnel, public relations and administration departments all in one. By December 1945, eight more Arizona hospitals received Blue Cross approval, in addition to the three original ones. Over 19,000 people were enrolled through groups and more than $43,000.00 had already been paid out in hospital bills for the care of its members. The plan's income that year was $83,610.94. During this period of early growth however, Don was confronted with another major problem, which, if not resolved, would perhaps scuttle all of his previous efforts and the progress thus far attained.

About the end of 1944, Arizona Blue Cross had received notification from the Attorney General's office, by way of a written opinion, that the original Arizona Hospital license to operate, having been granted under the Arizona non-profit law, was, in his opinion, inadequate and that the present Blue Cross Plan was not properly licensed under this law. This, of course, put the new plan in a precarious position legally. Once again, the glow of midnight oil could be seen in the Blue Cross office and a solution was compounded. In early 1945 the Arizona Medical Association, with the support of the Blue Cross member hospitals and the Arizona Blue Cross Plan, sponsored a special Enabling Act in the special session of the 17th Legislature then convening. Although there were times during these legislative sessions that success appeared doubtful, the Act was passed and became law under Gov. Sidney Osborn's signature on October 3, 1945. Licensure under the new law assured the Blue Cross Plan of a firm legal foundation.

Having weathered this storm, L. Donald Lau went back to the business at hand. Under his watchful eye, Arizona Blue Cross grew in stature and reputation. By 1946, the plan had increased its membership to over 37,000 and had paid out in excess of $124,000.00 for the year in hospital bills for members' care. Many satisfactory comments were being heralded from all quarters. The doctors were content, the hospitals, through Blue Cross payments, were meeting their financial obligations and the people of Arizona had, for themselves, a satisfactory, workable prepayment health care plan to meet unexpected hospital bills. But it wasn't enough. The population of Arizona, particularly Phoenix and Tucson, meanwhile having increased tremendously and destined to become a "new home" for hundreds of thousands more to come. it was necessary that a more comprehensive program be considered to meet the public need. Blue Cross was entirely adequate for hospital care. What the public wanted was a similar arrangement to help pay for unexpected surgical bills.

As a result, Arizona Blue Shield was born and sponsored by the Arizona Medical Association. In their meeting of June 22, 1946, it was moved, seconded and duly voted that the Association, acting through its House of Delegates, form a corporation under the new Arizona Nonprofit Hospital and Medical Service law, for the purpose of establishing a medical service plan for the State of Arizona, to be administered jointly with the Blue Cross Plan and under the direction of L. Donald Lau as executive director for both plans.

Once more, Lau was destined to hit stormy seas, this time of cyclonic proportions. Many of the medical doctors, having returned to private practice from active service, were uninformed of the latest change in medical economics and lacking the knowledge, understanding the

proper viewpoint of a physician's participation in a plan such as Blue Shield, protested vigorously and vociferously. Armed with patience and perseverance, plus a thorough, convincing knowledge of the advantages and benefits derived from this nationally proven method by both patient and doctor, Don Lau gradually overcame the antagonism shown the Arizona Blue Shield Plan. When the storm subsided and Blue Shield enrollment was opened to the public in November 1947, 53% of the licensed doctors of medicine in Arizona had signed participation contracts. In order to receive Blue Shield Commission approval, it was necessary that 50% of the medical doctors participate in the plan. The figure was close.

Today, over 95% of our Arizona Medical Association members are Blue Shield Participating Physicians. Membership in the plan, as of March 31, 1951, stood at 72,879. In a matter of three short years, Blue Shield has paid $991,-428.27 to its doctors for members' care—$493,-981.78 of this amount was paid in 1950 alone, representing a return of 90.4 cents out of every dollar paid into the plan for the year.

In turn, Arizona Blue Cross has become a million-dollar enterprise. Out of $1,308,504.54 income for 1950, $1,053,346.15 was paid to hospitals last year for members' care—or a return of 83.7 cents out of every dollar paid into the plan. As of March 31, 1951, Blue Cross has paid $3,476,057.80 to hospitals since its inception in 1944. Enrollment figures as of the same date show 122,589 members—and both plans are continuing to grow. The present Blue Cross-Blue Shield offices, as compared with their humble beginnings, now consumes the entire second floor of the Arizona Title Building. The present staff consists of 55 capable employees.

At a meeting of the Blue Cross District Nine Policy-Making Body, held in Little Rock, Arkansas in February 1951, Lau was elected General Chairman of the District, a responsibility requiring his direction of the district's over-all program for the coming year. (Blue Cross District Nine consists of the 10 plans in the Southwestern States of Kansas, New Mexico, Texas, Oklahoma, Missouri, Colorado, Wyoming, Arkansas and Arizona.) He has also been chosen Blue Cross alternate delegate to the American Hospital Association.

The most recent accomplishment of Arizona Blue Cross-Blue Shield has been the winning of national honors for outstanding achievement in public relations during the past year. The "Oscar" was presented to the Plan at the National Blue Cross-Blue Shield Enrollment and Public Relations Conference, held in Chicago last month (July).

Tirelessly, and with little thought of his personal comforts, Don Lau has carefully nurtured these "adopted children" through juvenescence into a healthy maturity, taking their rightful place as full grown members of the health care trial—the Medical Profession—the Hospitals—and Blue Cross-Blue Shield, a powerful public influence nationally and our strongest supporting force to keep medicine free from political contamination.

The task has been great—the accomplishments, many. We have chosen our guardian well.

Perhaps the very title of this editorial, although descriptive and befitting to the individual, may not be, on second thought, sufficiently adequate—a better one might conceivably be "Mr. Accomplishment."

TOPICS OF CURRENT MEDICAL INTEREST

RX, DX, AND DRS.

By GUILLERMO OSLER

WHAT SHOULD A DOCTOR DO about Medicine during his vacation? . . . Forget it? Avoid it? Ignore it? . . . Should he study it, review his plans, see other methods of practice? . . . Should he keep in touch with certain patients? Is he indispensable to some? Will a few wander away? Should he care? . . . Should he spend time on physical exercise? Get more rest? Try a change? Travel? Be with the family? . . . Tough problem. Should I be wondering about it on a vacation?!

The IMPROVEMENTS IN PENICILLIN are now being more certainly defined. They hugely reduce the allergic effect—a complication which follows in 6 to 10 per cent of the ordinary usage. . . . Several workers have described preparations which seem to be hypo-allergenic, and also desen-

sitizing. . . . One is a biosynthetic analogue (cousin) and the others are salt (relatives by marriage). . . . They are therapeutically equal to the standard penicillins.

The NAMES which are given to most of the TRADE-PREPARED DRUGS are quite mystifying. One wonders why they were chosen—and also what they mean. . . . It must be hard eternally to be original and simple and graphic in such a crowded field. An example of success could be 'Sulfabiotic'; it is a combination of sulfonamides and penicillin, and one can guess it from the name. . . . On the other hand we have 'Pabalate', 'Priscoline', and 'Tromexan'. 'Pabalate' could mean a new form of baby food, but it is a combination of para-aminobenzoic acid and sodium salicylate. 'Priscoline' doesn't suggest the drug (benzazoline) or its use as a vasodilator. 'Tromexan' sounds like a foot-powder from below the Rio Grande—instead of an anticoagulant. . . . What those companies need is someone who can make puns.

The report of Russek and colleagues in a recent JAMA should help resolve the ANTICOAGULANT-MYOCARDIAL INFARCTION problem, since most of us hate to use a hazardous drug in the absence of laboratory controls. . . . They divided their intreated cases according to the presence or absence of CRITERIA WHICH WOULD GIVE A GUARDED PROGNOSIS,—1. previous infarction; 2. intractable pain; 3. extreme or persisting shock; 4. notable cardiac enlargement; 5. gallop rhythm; 6. congestive failure; 7. auricular fibrillation or flutter, ventricular tachycardia, and intraventricular block; 8. diabetic acidosis or other serious disease. . . . More than 200 patients had NONE of the reasons for guarded prognosis; the mortality was 2.45 per cent, and the incidence of thromboembolic disorders was less than 1 per cent. More than 200 other patients had ONE OR MORE signs of unfavorable prognosis; 44.5 per cent died, and 7.7 per cent had thromboembolism. . . . The conclusions suggest that Dicumarol need only be used in those cases in which the signs and symptoms suggest a poor prognosis without it.

The DRUG-HOUSES have been given quite a few laurel wreathes in this column. Many of them rightly should stand high with the profession and the purchasing public. . . . Now we find an accolade from a more cold-eyed source,—reports from two of the best-known investment trusts, containing data on their increased holdings of Merck, Park Davis, Pfizer, and other similar stocks.

Anderson and Priestley of the Mayo Clinic have reported the incidence of infection in CHOLEDOCHAL BILE at the time of operation in the biliary tracts of 100 patients. . . . Seventy per cent had stones in the common duct, and 75.7 per cent of these had bacteria in the bile. Thirty per cent had no stones, and had only 50 per cent infection. . . . Bacteria are found more often in cases which had previous surgery, and in cases with chills and fever. The organisms are those commonly found in the intestinal tract. . . . They do not believe that infection can be considered a notable factor in the formation of stones. . . . They suggest that antibiotics be used to clear the tract of infection, especially after tubes have been removed.

Probably only a few physicians know or care much about CEREBRAL ANGIOGRAPHY. . . . A sure sign of its progress, however, is a report at a recent x-ray meeting on "LOW-COST Cerebral Angiography". . . . The more it's needed the more it's studied the lower the cost becomes, sure as shooting. And the same in reverse order.

Price and Binns have found demonstrable SINOBRONCHITIS in 37.7 per cent of a large series of Pittsburgh children who were hospitalized for chronic respiratory symptoms. . . . They tried out four routines of treatment on a later series, and found the best results from a combination of an oral antihistamine, oral or slow-absorption parenteral penicillin, aerosol penicillin, and decongestant-penicillin nosedrops. . . . The nosedrops were required in order that the aerosol could be inhaled thru the nose.

An editorial in the Journal of Pediatrics reminds us that the word 'RESEARCH' comes from the Latin 're' (again) plus 'circare' (to go around). . . . The lower forms of research, in which ideas of others are reviewed or analyzed or appraised, conform to the origin of the word quite well. They are truly a 'go-around'.

FORTUNE Magazine has analyzed the subject of ADRENAL CORTICOID MATERIALS as no medical journal could. . . . Their Science, Economics, and other editors have analyzed the background, the personalities involved, the manufacture, and the future of both American and Mexican drugs. . . . A beautiful article, and one which should give us data from which to predict. It looks like better drugs, new drugs, and lower cost.

TIME Magazine finds interesting THE THEORIES OF DR. REUBEN KAHN, the serologist from Michigan. . . . Dr. Kahn's dreams have been in the same pattern as his test for syphilis,—More diseases should produce some evidence of their presence. . . . The results of the dream and work are now available as a Commonwealth Fund Publication "An Introduction to Universal Serologic Reaction in Health and Disease". . . . The pattern in disease must have a contrast with the pattern in health.

'HOSPITAL TOPICS' (and 'LOOK' Magazine) describe a "Rehearsal for A-Day", at the Massachusetts General Hospital. They have arranged

to move 930 patients into the suburbs as a part of a civil defense plan. . . . In practice they used loud-speakers, moving vans, cars, station-wagons, and volunteer drivers. They 'tagged' staff-members and used them as patients. Teams of nurses and physicians cared for groups. . . . Among the odd pieces of practical information,—station-wagons with mattresses on the floor are not satisfactory vehicles for the seriously ill; almost all of the furnishings of a hospital can be transported in moving vans; and, unless the hospital has 3 hours of warning, it might better have "stood in bed."

A study of 300 unselected surgical patients was made in the anaesthesia department at Harvard to determine the frequency of obvious or silent ASPIRATION OF THE STOMACH CONTENTS DURING ANAESTHESIA. Evans blue dye was placed in the stomach (by gastric tube or a capsule) 15 to 30 minutes before induction. The mouth, pharynx, larynx, and bronchi were inspected after operation. . . . Regurgitation occurred in 26 per cent of the patients, and 16 per cent aspirated gastric contents into the lung. Frank vomiting occurred in only 8 per cent. Aspiration was twice as frequent in the frank emesis as in the silent regurgitation. . . . Regurgitation occurred more often in the Trendelenburg and lateral positions. It was more frequent in the patients handled by inexperienced anaesthetists. Gastric tubes exert a protective effect by reducing the volume of gastric contents.

Dr. Baketel, an editor of 'Medical Economics', says that THE CHIEF INTEREST OF A PATIENT is not in a doctor's reputation, nor in his fee, but in the person who will take the greatest interest in him.

After all the controversy over the THERAPY OF SYPHILIS and neuro-syphilis (which few physicians ever see anymore), it is good to find several definite summaries. . . . E. W. Thomas of New York says that early acute syphilis may best be treated by 1,200,000 units of procaine penicillin in oil and aluminum monostearate on the first day, and 600,000 units per day for five days. Therapy over several weeks has no advantages. . . . Late syphilis (other than CNS disease) may be treated with 600,000 units per day for 15 days. . . . Relapses should be treated with doubled amounts of penicillin. . . . Curtis, Kitchen, O'Leary, Hattner, Rein, Schoch, Shaffner, and Wile say that accumulated experience shows the superiority of penicillin alone, and that heavy metals are unnecessary in the vast majority of cases.

COMING TO TERMS,—

The American Review of Tuberculosis insists that its abstracters use the words 'roentgenogram', 'roentgenography', etc. . . . This is fine tribute to Roentgen, but the whole world now accepts the much simpler 'X-ray', both as a noun and verb.

The tuberculosis, thoracic, and medical societies are all agreed on the usage of 'tuberculous' (adj.,—a lesion or infection or condition caused by the tubercle bacillus), and 'tuberculosis' (noun,—disease, caused by the tubercle bacillus). . . . The lexicon of newspapers is stuck with the one (wrong) word, 'tubercular', which simply means 'nodular'.

HUMAN MYIASIS FROM THE SCREWWORM FLY IN ARIZONA

(With Report of an Illustrative Case Caused by *Callitroga americana C. & P.*)

John Emmett, M.D., Epidemiologist and Russell E. Siverly, Entomologist*

Infestation of the body with the maggots of flies (myiasis) remains unusual enough to evoke interest in all concerned. Myiasis may be caused by many species of flies and, depending on the species, may occur in the skin, in the genito-urinary and intestinal tracts, in the eye, in and about any of the bodily orifices and in exposed tissue such as wounds and the lesions consequent to syphilis, tuberculosis or epitheliomas.

In 1907 Yount and Sudler (1) collected records of 23 cases of human myiasis which occurred in Arizona within one year and in 1927 Stroud (2) added 16 more seen in 13 years of practice. Records of a hospital in Phoenix show three admissions for myiasis in the past two years. The disease is more common than the literature would indicate and it is considered timely to present this review and report a recent case in which the causal fly was accurately identified.

Of the 39 Arizona cases, 30 (77%) were nasal infestations. Four occurred in superficial wounds, 2 in skin (axilla and wrist, probably the sites of furuncles), 1 in a carcinoma of the cheek, 1 in a "specific sore" on the cheek, and 1 in an area of gangrene of the heel.

Practically all of the nasal cases suffered from predisposing nasal disease as did the case reported below. Among the diseased conditions reported are epithelioma, chronic syphilitic rhinitis (6 cases), severe chronic rhinitis (etiology unclassified), chronic nasal catarrh, and "an old

*From the Communicable Disease Center, Public Health Service, Federal Security Agency, Phoenix, Arizona.

diseased condition of the nose which had destroyed the septum." Practically all cases, save for the rare accidental inhalation of a blowfly while awake, were infested while sleeping outdoors in the daytime. Males were more commonly affected than females, presumably because of their work. Any age group may be infested, but there is a preponderance of cases among adults of 40 and above.

There were five deaths among the 39 *cases,* a mortality rate of approximately 13%. All occurred in nasal infestations. Three of the deaths were directly attributable to the depredations of the larvae. (Autopsy on a fatal case recently seen in Phoenix revealed screwworms in both antra, in the sphenoid and ethmoid sinuses, and in the esophagus and stomach.)

The symptoms of nasal myiasis include epistaxis, severe pain, (sinuses, nose, orbital, etc.) nasal discharge, reddening and swelling of mucous membrane and/or the face, fever, restlessness, anxiety and depression. Photophobia and conjunctivitis have been described.

Treatment usually consists of the exhibition of chloroform (from 25% diluted in olive oil to full strength), as sprays, douches or packs. Chloroform stimulates the larvae and facilitates their removal by forceps. The mucous membrane of the nose or soft palate has been incised under local anesthesia and the larvae moving beneath extracted. In cattle, the disease is now treated by a new preparation of the Department of Agriculture called "Smear EQ 335" which is applied topically and contains the larvicide, lindane.

The Arizona cases were "screwworm" infestations ascribed to *Chrysomyia macellaria* (Fabr.). The genus is now called *Callitroga* (formerly *Cochliomyia* or *Chrysomyia* or *Compsomyia*) and contains two myiasis producing species, *Callitroga americana* (Cushing & Patton), the primary screwworm fly, and *Callitroga macellaria,* the secondary screwworm fly. The primary screwworm fly was first described in 1933 by Cushing & Patton (3) and it is now believed that most of the infestations prior to 1933 reported as *C. macellaria* were in reality caused by *C. americana.*

Screwworm flies are blowflies, slightly larger than houseflies, with yellow to orange heads, and a metallic, irridescent, blue-green body. The thorax is marked with three distinct, longitudinal, dark stripes. In the United States these flies are more prevalent in the South and Southwest in the warmer parts of which they may breed all year round. According to Knipling and Travis, continued cold (minimum 20°-47°F, maximum 33°-65°F) kills most if not all adults in nature. Screwworms attack cattle primarily, but horses, sheep, swine, dogs, deer, rabbits, opossums, domestic turkeys, and other animals have been reported infested (4, 5). The female of the primary screwworm fly selects living tissue (wounds) in which to oviposit while the secondary fly seeks *carrion.* Three and four hundred eggs may be deposited at a time. These are readily visible with the naked eye. Knipling (6) states that the eggs of *C. americana* may be distinguished from those of *C. macellaria* by being whitish and laid in compact, oval, shingle-like masses glued to the edges of the wound or on dried blood clots or scabs. The eggs of *C. macellaria* are more yellowish and less compact. The eggs of both species hatch within a few hours, varying with conditions of temperature and humidity. Each egg yields one larva or maggot which is off-white in color and about 17mm. in length when mature. The dark, pigmented, tracheal trunks of *C. americana* larvae aid in differentiating them from those of *C. macellaria* in which the tracheal trunks are unpigmented. The larvae burrow into the tisues of animal or man on which they feed, reaching maturity in about 5 days. At this time, if possible, escape is made into the ground, it being necessary that the larvae seek a drier medium in which to pupate. In nature the pupae are dark brown to black. Under favorable conditions pupation requires about 9 to 14 days at the end of which time the young fly emerges.

The myiases seem most clearly classified according to the method of Patton based on the biological requirements of the fly (7). He describes three groups:

Group I

Specific myiasis producing Diptera "whose larvae are found only in living tissue." These are the obligatory parasites hence the most dangerous to animal and man. Here belongs the primary "screwworm fly," *Callitroga americana.*

Group II

Semispecific myiasis producing Diptera which includes those flies that normally breed in dead animal tissue but that occasionally may infest diseased tissues of animals and man. Here be-

longs the secondary "screwworm fly," *Callitroga macellaria.*

Group III

Accidental myiasis producing Diptera, the larvae of which only occasionally and accidentally enter the human body. The house fly is included here and it and many of the other included species may breed in substances used by man as food. They therefore are the usual vectors in cases of gastro-intestinal myiasis but certain species may enter the urethra and bladder and, rarely, may infest wounds and the orifices about the head.

For details of species and of the types of myiasis they cause, the reader is referred to the United States Department of Agriculture publication No. 631, *Flies That Cause Myiasis in Man* by Maurice T. James.

Prevention:

As pointed out by *Dove* (8), the control of myiasis in cattle decreases its incidence in man. There were 55 cases reported from the Southeastern States in 1935, when the incidence of screwworm infestation in livestock was high. The next year when the incidence was low in livestock it was also low in humans, only eight cases being reported.

The proper treatment of chronic nasal disease is most important for this will remove predisposing factors. Protection of open wounds is likewise important. Avoidance of sleeping outdoors in the daytime and the screening of houses to keep out flies obviously are applicable measures. The use of a headnet to prevent screwworm infestation has been suggested but hardly seems practical.

Illustrate Case Report:

The patient is a 70-year-old white male with a long term history of "sinus trouble," recurrent epistaxis and ozena due to atrophic rhinitis. For several years he has sneezed "100 times a day," passing "scabs" from the nose.

On admission to hospital (November 8th) his complaints were uncontrollable nosebleed which had started on the morning of November 6th and severe pain involving the nose and right orbital area. There was associated fever, anxiety and depression. He gave a history of having taken a noon-day nap in his home on November 5th and further recalled having noted a "green blowfly" in the room.

Physical examination revealed an anxious, febrile white male with atrophic rhinitis, ozena and evidence of recent epistaxis. The right side of the face (infraorbital and maxillary areas) was reddened, swollen and tender.

On November 10th screwworm larvae were expessed from the nose during an episode of violent sneezing. With subsequent treatment (direct application of chloroform and local recovery with nasal forceps) an estimated 200-300 larvae were retrieved and the patient made an uneventful recovery. Larvae had invaded the sphenoid sinuses and one eustachian tube.

Specimens of the larvae were identified and confirmed* as being those of the primary screwworm fly, *C. americana.* On November 10th, several of the larvae were placed in soil and pupation occurred during the subsequent 24 hours. Emergence has not occurred in 100 days.

An investigation of the patient's premises and surrounding area was made on November 13th. The patient lived in one of the small aggregation of frame houses in a rural village populated mainly by agrarian workers. There were several head of stock in the neighborhood but no domestic animals on the immediate premises. Some 2 miles east of the patient's dwelling there is a large cattle ranch where screwworm infestation reportedly occurred. With the cooperation of the ranch management an infested steer was examined, and eggs, larvae, and one adult (female) were collected. The eggs were placed on nutrient and blood agar, but failed to develop. The larvae, and the one gravid female were identified and confirmed as *C. americana.*

To recapitulate, larval specimens of *C. americana* were recovered from the nasal passages of the patient. This species is indigenous to the area in which the patient lived, and specimens were collected at a site within normal flight range of *C. americana* from the patient's home (9). In addition, the patient reported dressing a deer at his homesite on November 4th. The resultant odor conceivably attracted blowflies to the immediate area.

SUMMARY:

1. Thirty-nine cases of human myiasis reported from Arizona are reviewed.

2. The relationship of the primary and secondary screwworm flies is discussed, their life cycles reviewed, and Patton's classification of the myiases cited.

3. A characteristic case is reported in which the causal fly was identified as *Callitroga americana.*

Acknowledgements:

Grateful acknowledgement is made to Dr. H. R. Dodge of the Comunicable Disease Center, Atlanta, Ga., for his confirmation of the identities of larvae and fly; to Dr. J. Brooks of Phoenix, Ariz., for his cooperation in allowing us to study and follow his interesting case; and to Dr. M. Rosenthal of Phoenix for giving us access to his protocol of the autopsy which he performed on the fatal case of myiasis cited above.

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BOOK REVIEWS

"Physiology of the Eye: Clinical Application" by Francis Heed Adler, M.A., M.D., F.A.C.S. Pp. 709 with 319 illustrations, 2 in color. Price $12.50. Published by C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Missouri. 1950.

The author's long experience as teacher in physiology and ophthalmology at the University of Pennsylvania and his comprehensive knowledge of each of the basic subjects contained in his book, combined with his research ability make him ably qualified for such an undertaking.

Beginning with the eyelids Chapter I, to the final chapter on Binocular Vision, the author's skill and ingenuity portrays his special interest in this field. The chapters dealing with the aqueous humor and the intra ocular pressure well bear that out. Also, Dr. Adler's differential diagnosis of paresis of the superior rectus and the superior oblique muscles make it very clear for the average reader.

This book is most beautifully and instructively illustrated. The bibliography given at the end of each chapter shows how much work the author has done and due credit is given for the help he received from various contributors.

The clinical application of this book in general medicine is well brought out when the author states "one of the characteristic signs of diabetic coma is a very low intra-ocular pressure. The eyes feel mushy soft and the diagnosis can almost be ventured from this sign alone. The low pressure is probably due to an increase of crystalloids in the blood for this is kept fairly constant, an increase in glucose ketonic acid being compensated for by a corresponding loss of chlorides." Another example, the frequent complaint of annoying twitching of the eyelids one encounters in the practice of ophthalmology, the author advises small doses of quinine for this spasm.

Dr. Adler's style and methods of presentation of the twenty-two chapters, arranged in a conventional sequence with such a degree of clarity, make this an excellent text and one which can be highly recommended.

H. J. French, M.D.

"Principles and Practice of Surgery." By: Jacob K. Berman, A.B., M.D., F.A.C.S., Associate Professor Surgery, Indiana University School of Medicine, Indianapolis, Indiana. Cloth $15.00. Pp. 1378 with 429 illustrations. The C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, Missouri. 1950.

This excellent volume appears to have well filled its aim of correlating the basic sciences to the fundamental principles of surgery, and can accordingly be highly recommended as a text for students, as well as a fine completely new abreviated reference for the busy general surgeon.

Its arrangement is in five sections:—General Considerations of Surgical Principles, Local Response and General Body Reactions to Injury, General Reactions to Injury, Reactions of Tissues and Organs to Trauma of Unknown Origin, and lastly Diseases and Injuries of Specific Organs and Systems."

It is refreshing to find a textbook rather well represented in all the newer surgical fields such as in cardiac and blood vessel surgery; also such operative techniques as vagotomy are covered.

While some might question discussion of the gallbladder and bile ducts under the gland section instead of the alimentary section, it is well covered with the liver and pancreas.

On the whole then this is an extremely fine new textbook of general surgery well organized and arranged and with ample references given so that the student may pursue each subject further. It is highly recommended.

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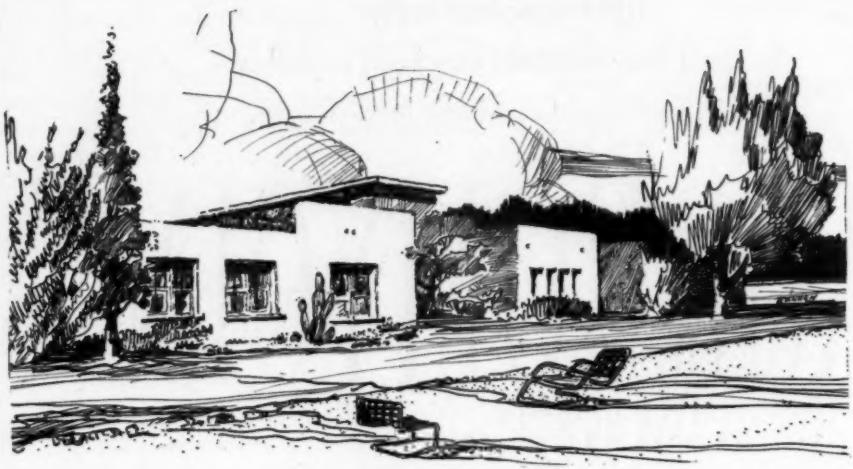

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NEWS ITEMS

Do you know that the National Board voted a scholarship of $500.00 to the Careers for Nursing, and that the auxiliary delegates voted at convention to contribute $10,000. to the National Fund for Medical Education, and $100 to the World Medical Association?

——o——

A revised list of "Sources of Motion Pictures on Health" has been prepared by the Committee on Medical Motion Pictures of the American Medical Association. This new mimeographed list includes 9 pages of addresses of the major loan and rental libraries, the state health departments' film libraries and references to printed lists and catalogs. Copies are available from:

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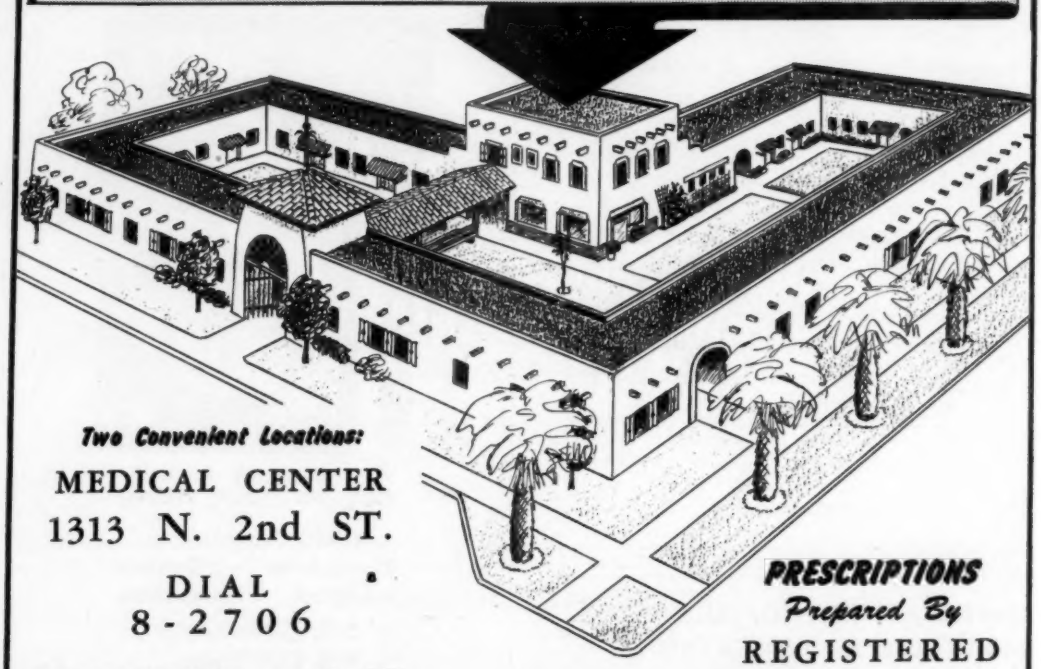

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What is Civilian Defense? It is just what it sounds—civilians who have banded together to defend and protect themselves from an attack or disaster. As the world situation stands today, civilian defense should be supported by more than a few individuals who are far-sighted enough to see the tremendous job of organization involved—it should be supported by all of us working together. Should atomic war suddenly explode in our faces, which we devoutly hope will not happen, the Red Cross, the hospitals, and our medical societies will all call upon us to help them. To be of use in such an emergency we should be prepared.

First, let me give you a blue print of what has been done. The United States government has spent much time and money on writing the ideal civilian defense setup. It has compiled the research of its army medical department, and evaluated the defense efforts of England and other European countries in the last war. These have all been sent to the governors of the individual states. The A.M.A. has compiled a tremendous amount of material from studying the reports on what happened to the population of Hiroshima. The A.M.A. has figured what health and emergency services we would need, if subjected to atomic attack, and how many volunteers are necessary to run such health services. These reports have been sent to all the medical societies in the country.

At this writing, the governor of Arizona has appointed Mr. George B. Owen, in Phoenix, state civilian defense director. He, in turn, has appointed a special staff of ten people to coordinate the efforts of the state. In charge of health is Dr. Joseph M. Greer, assisted by Dr. C. G. Salsbury. These are all recent appointments, and the organization is just starting. As Arizona is not designated a primary target—in other words a place where an atom bomb is likely to be dropped—we have been slower than some of the coastal and industrialized states in organizing. The wheels are now beginning to turn, and while waiting for an appointed role, we can also become ready.

We can become informed in what can be done to protect ourselves in an atomic attack. It is possible to protect yourself; you don't have to close your eyes and go around hoping that it just won't happen here. There is an article in LIFE magazine, which the editors are glad to send anyone for a few cents, which outlines very simply a few basic steps anyone can take to protect himself. The NEW YORK TIMES also has a pamphlet of reprints, from a series of articles it published, entitled "We Are Not Helpless," which they will send you for ten cents. Your medical society has many articles which give important information, although in somewhat more technical terms. By reading these throughout the Auxiliary membership, we can become informed, and thereby help prevent a disastrous panic should an attack actually occur.

Investigation has disclosed that one of the causes for large numbers of casualties at Hiroshima was the lack of common knowledge of first aid. The many articles I read all stressed the importance of everyone knowing first aid, especially for flash burns. Here is something all the members of the Auxiliary and the members at large can do—become proficient first aiders. If you had a course in the last war, renew it; if you have not had a course, your local Red Cross organization will be happy to furnish an instructor.

Many additional nurses and nurses aides would be needed immediately, should atomic warfare reach our shores. There may be nurses in the Auxiliary who have not practiced their profession since they were married; these could offer their services should an emergency arise, or become members of the Red Cross teaching staff. Some, who may have let their certificates lapse, could renew them and then would be in a position to help in the same way. Those of us who have not had nurses training could take advantage of the excellent courses which the Red Cross give and become nurses aides or home nurses.

There are several movies on the atom bomb and atomic bomb defense which it would be possible to obtain, either through writing your state medical society or the civilian defense director. These might be a good way to interest the membership in civilian defense.

If you are a member at large, wishing to be of service to your community, your state director of civilian defense stands ready to offer sug-

gestions to you. If you are a member of a county auxiliary, your medical society will have a doctor in charge of civilian defense. Contact him. At all times your program chairman will be glad to offer any assistance possible. Remember, however, that the important thing for us, as doctor's wives, is to prepare ourselves and assist our communities to the best of our ability.

POLIO POINTERS FOR 1951

Reprinted in part from the BULLETIN—

If Polio comes—

DO Allow children to play with friends they have been with right along. Keep them away from new people, especially in the close daily living of a home.

Because—Once polio has appeared in a community, scientists say the virus probably is widespread. Your children probably have come in contact with it already and developed a degree of resistance to that particular virus.

DO Wash hands carefully before eating and always after using the toilet—especially important when polio is around. Also keep food clean and covered.

DO Watch for signs of sickness, such as headache, fever, sore throat, upset stomach, sore muscles, stiff neck, extreme tiredness or nervousness, trouble in breathing or swallowing.

DO Put a sick person to bed at once, away from others, and call the doctor. Quick action may lessen crippling.

DO Telephone your local Chapter of the National Foundation for Infantile Paralysis, if you need help. Locate through telephone book or health department. No patient need go without care for lack of money. Your Chapter will pay what you cannot afford. Because—The 2800 local chapters of the National Foundation, supported by your contribution to the March of Dimes, exist for this purpose. Other March of Dimes funds are spent for scientific research and the training of much-needed personnel.

DO Remember, at least half of all polio patients get well without any crippling.

Because—Recent surveys show that 50% of all diagnosed polio cases suffer no paralysis at all. Another 25% recover with no disabling aftereffects. 15% are severely paralyzed, and about 8% die.

DON'T—get over-tired by hard play, exercise, work, or travel. This means men, women, and children.

DON'T—get chilled. Don't bathe or swim long in cold water, or sit around in wet clothes.

DON'T—have mouth or throat operations during a polio outbreak.

DON'T use another person's towels, dishes, tableware, or the like.

DON'T—take children to places where there is polio.

DON'T—take your child out of camp or playground, where there is good health supervision.

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IF YOUR A.M.A. JOURNAL IS MISSING

Recently the Executive Office of the Society has received a number of telephone calls from members asking the question, "I haven't been receiving the J.A.M.A. for the last few weeks. I sent in my check for $25 for A.M.A. dues on such-and-such a date. What has happened?"

Investigation reveals that these calls usually are from members who did not pay their 1950 A.M.A. dues by the deadline date of December 31, 1950, and who have since sent in their checks for 1950 on say—January 15, 1951.

What has happened is quite simple. When the 1950 dues were not paid by the end of the year the doctor entered the category of delinquent membership in the A.M.A. His name was removed from the roster of members and his name was removed from the list of those who receive the Journal of the A.M.A.

Such delinquent members will not be entered on the circulation list of the Journal of the A.M.A. until they have been reinstated to full membership. This means they must pay BOTH their 1950 and 1951 dues. If they have now paid their 1950 dues (after Jan. 1, 1951) they must also pay the 1951 dues before they enter status of member in good standing. Until then they will not receive the Journal.

Word direct from the A.M.A. is that members who paid their 1950 dues on time (before the end of the year 1950) are in good standing and have until the end of 1951 to pay their 1951 dues. They are considered as 'good circulation risks' and will continue to receive the Journal during 1951 even if they cannot pay their 1951 A.M.A. dues until later this year.

BUT members who did not pay their 1950 dues on time are now delinquent. They are not considered good circulation risks and the Journal will not be sent to them until they enjoy full reinstatement by paying both 1950 and 1951 dues.

It was explained in the circular which accompanied the bills for A.M.A. dues that both 1950 and 1951 dues must be paid. The penalty for those who did not read this, did not believe it, or did not act upon this advice is the penalty of not receiving the Journal of the A.M.A.

When a member pays his full dues and is reinstated in the A.M.A. his subscription to the Journal will start again. And the reinstated member can write directly to the Office of the J.A.M.A. and ask for back copies that he has missed.

We are informed that the Journal printed a number of extra copies of the early issues of 1951 to cover just this possibility. But the extra supply is limited and there can be no guarantee that the supply will not be exhausted.

To repeat the main point:

A.M.A. members who paid their 1950 dues during 1950 have no need to worry. Their J.A.M.A. will keep coming to them throughout the year. But they must pay their 1951 A.M.A. dues during 1951, quite naturally.

Members who have not paid their 1950 A.M.A. dues until after January 1, 1951, are temporarily NOT receiving the Journal and this is one of the penalties they pay for being delinquent.

Already a few calls have come from delinquent members who have now paid their 1950 and 1951 A.M.A. dues and cannot understand why they do not immediately receive the A.M.A. Journal the following week after they write out their checks. To these physicians it may be of interest to know something of the process of reinstatement.

For example, thousands of checks from members come to the County Society for payment of A.M.A. dues. After opening the envelopes and sorting out the checks, the proper amounts must be entered upon individual treasurer's cards for the permanent records. Lists of names of members paying dues must be arranged in alphabetical order for the auditors. Each check must be stamped for deposit, and deposit slips filled out and rechecked again. The money for A.M.A. dues thus enters the bank to the account of the County Society.

All these operations, including still others, are simultaneously going on to record the payments for County and State dues which are handled separately.

Following such activity at the level of the county society alphabetized lists of members who have paid their A.M.A. dues are sent to the Medical Society of the State of New York together with a check to cover payment of such dues. The State Society, in its turn, must enter the information on its cards, prepare audit lists, make deposits and maintain its own set of records.

Next the State Society sends to the A.M.A. lists of members who have paid their A.M.A.

dues and sends covering checks for each such list.

In its turn the A.M.A. must enter all information on its own cards and—along the way—notifies the A.M.A. Journal that member X, for example, is now in good standing. If member X's name has been removed from the mailing list of the J.A.M.A., because he was delinquent, a new addressograph plate must be prepared with his name and address so that labels can be printed to mail his magazine. Since these labels are prepared an issue or two ahead of mailing it thus takes several weeks to start the machinery flowing again at the Journal office.

All these steps—at the county level, at the state level, and at the national level—provide an explanation of why it is impossible to expect that as soon as a check is mailed to the N. Y. County Medical Society the Journal of the A.M.A. will arrive the next week.

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*Baumgartner, L.: Wider Horizons for Children; The Mid-century White House Conference and Children's Nutrition, J. Am. Dietet, A. 27:281 (Apr.) 1951.

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